EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/496213/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tyverb

International non-proprietary name: LAPATINIB

Procedure No. EMEA/H/C/000795/II/0022

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACSR / aCSR Abbreviated Clinical Study Report
AE Adverse event
AKT 58kDa serine/threonine protein kinase B (PKB)
ALP Alkaline phosphatase
ALT (SGPT) Alanine aminotransferase
ALTTO Adjuvant lapatinib and/or trastuzumab treatment optimization
ANC Absolute neutrophil count
AST (SGOT) Aspartate aminotransferase
ATC Anatomical therapeutic classification
β-hCG Beta human chorionic gonadotropin
BOND Bowel Oncology with Cetuximab Antibody
CBR Clinical Benefit response Rate
CI Confidence interval
CNS Central nervous system
CR Complete response
CSR Clinical Study Report
CT Computerized tomography
CTC Common toxicity criteria
CTCAE Common terminology criteria for adverse events
dL Deciliter
DOR Duration of Response
ECD Extracellular domain
ECG Electrocardiogram
ECHO Echocardiogram
ECOG Eastern Cooperative Oncology Group
eCRF Electronic case report form
EGFR Epidermal Growth Factor Receptor, also known as ErbB1 or HER-1
ER Oestrogen receptor
ErbB1 EGFR, c-ErbB1, HER-1
ErbB2 c-ErbB2, also known as p185
ELISA Enzyme-linked immunosorbent assay
FACT-B Functional assessment of cancer therapy-breast
FACT-G Functional assessment of cancer therapy-general
FDA Food and Drug Administration
FISH Fluorescence in situ hybridization
GCP Good clinical practice
GSK GlaxoSmithKline
HER2 c-ErbB2, also known as p185
HLQ Higher limit of quantification
HPLC High Performance Liquid Chromatography
ICF Informed consent form
IEC Independent ethics committee
IgM Immunoglobulin
IHC Immunohistochemistry
IRB Institutional review board
IRC Independent review committee
ITT Intent-to-treat
IV Intravenous
IVR Interactive voice response
L Liter
LD Longest diameter
EGF104900
LLN Lower limit of normal
LLQ Lower limit of quantification
LOCF Last observation carried forward
LVEF Left ventricular ejection fraction
MAPK Mitogen activated protein kinase
MBC Metastatic breast cancer
MedDRA Medical dictionary for regulatory activities
mg Milligrams
mg/kg Milligrams per kilogram
mg/dL Milligrams per deciliter
mg/mL Milligrams per milliliter
mL/min Milliliters per minute
MRI Magnetic resonance imaging
MUGA Multigated acquisition
MS Mass Spectrometry
NCI National cancer institute
NOS Not otherwise specified
ORR Overall tumour response rate
OS Overall survival
OTR Optimally tolerated regimen
PD Progressive disease
PFS Progression-free survival
PgR Progesterone Receptor
PGx Pharmacogenetic
PP Per protocol
PR Partial response
QOL Quality of life
RAMOS Registration and medication ordering system
RAP Reporting and analysis plan
RECIST Response evaluation criteria in solid tumors
SAE Serious adverse event
SAG Scientific Advisory Group
SCE Summary of Clinical Efficacy
SD Stable disease
SOC System organ class
TKI Tyrosine-kinase inhibitors
TOI Trial outcome index
TTP Time to progression
TTR Time To Response
ULN Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd. submitted to the European Medicines Agency on 16 February 2012 an application for an extension of indication variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Tyverb	LAPATINIB	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with metastatic disease that has progressed on prior trastuzumab therapy(ies). Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/47/2008 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bengt Ljungberg Co-Rapporteur: Bruno Sepodes

Submission date:	16 February 2012
Start of procedure:	26 February 2012
Rapporteur's preliminary assessment report circulated on:	20 April 2012
Co-Rapporteur's preliminary assessment report circulated on:	30 April 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 May 2012
MAH's responses submitted to the CHMP on:	15 August 2012
(Co-)Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	4 October 2012
(Co-)Rapporteurs' final assessment report on the MAH's responses circulated on:	15 October 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	12 December 2012
(Co-)Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	4 February 2013
(Co-)Rapporteurs' final assessment report on the MAH's responses circulated on:	15 February 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	26 March 2013
(Co-)Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	13 May 2013
SAG experts meeting to address questions raised by the CHMP (Annex 6)	14 May 2013
(Co-)Rapporteurs' updated assessment report on the MAH's responses circulated on:	17 May 2013
An Oral explanation took place on:	27 May 2013
4th Request for supplementary information and extension of timetable adopted by the CHMP on:	30 May 2013
MAH's responses submitted to the CHMP on:	4 June 2013
(Co-)Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	13 June 2013
(Co-)Rapporteurs' updated assessment report on the MAH's responses circulated on:	24 June 2013
CHMP opinion:	27 June 2013

2. Scientific discussion

2.1. Introduction

Tyverb (lapatinib) is a reversible tyrosine kinase inhibitor that potently inhibits both epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Clinical evidence has shown the efficacy of lapatinib in HER2-positive breast cancer. Tyverb is currently approved for use in the following indications:

Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

• in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

• in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor. No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population.

Historically, cytotoxic chemotherapy has been an essential component of systemic palliative therapy for patients with metastatic breast cancer (MBC). However, several studies have shown that cytotoxic therapy in the absence of anti-HER2 targeted therapy in HER2-positive MBC has decreased efficacy (Cancello, 2008; Fabi, 2008; Park, 2009; Seidman, 2008; von Minckwitz, 2009), and is therefore no longer recommended as a standard of care for this patient population (National Comprehensive Cancer Network (NCCN) Guidelines, 2011; European Society for Medical Oncology (ESMO) Guidelines, Cardoso 2011; Japanese Breast Cancer Society Guidelines, 2011). Lapatinib and trastuzumab (in combination with chemotherapies) are both anti-HER2 therapies approved for the treatment of HER2-positive MBC. Trastuzumab is indicated as single agent, as well as in combination with other therapies, whereas lapatinib is only authorised for combination therapy.

The present variation application is to extend the indication of Tyverb for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with metastatic disease that has progressed on prior trastuzumab therapy(ies).

2.2. Non-clinical aspects

2.2.1. Introduction

The pharmacology, pharmacokinetics characteristics and toxicity of lapatinib have been assessed at the time of the initial marketing authorisation application (MAA). With this application only a small number of studies with direct relevance to the applied indication were submitted by the MAH.

Type of Study	Species (Strain)/ Test System	Method of Administration	Report No.
Lapatinib synergy with anti-ErbB2 antibodies	BT474 cell line	In vitro	RH2006/00067/01
Effects of lapatinib on phosphorylation, activity and expression of ErbB1, ErbB2, Akt and Erk1/2 and epidermal growth factor	S1, HN5, BT474 and HB4a cell lines	In vitro	RH2006/00066/01
Efficacy of lapatinib in combination with trastuzumab, vinorelbine, and gemcitabine	BT474, SKBR3, BT-TR and SK-TR SUM225 breast cancer cell lines	In vitro	2011N127934_00

2.2.2. Pharmacology

To support the mechanistic plausibility of the applied indication for Tyverb, the MAH presented data from two pharmacology studies previously submitted at the time of initial MAA and conducted with the lapatinib/trastuzumab combination as well as the results of one new primary pharmacology study:

- RH2006/00067/01 - Evaluation of the synergy of lapatinib with anti-ErbB2 antibodies

This study was conducted to determine whether the killing of ErbB2 overexpressing breast cancer cells could be enhanced by combining lapatinib ditosylate monohydrate with anti-ErbB2 antibodies,

trastuzumab, or polyclonal antisera generated by vaccination of rabbits with human ErbB2 fusion protein (pAb), following incubation for 72 h. Further examination of lapatinib and these antibodies effects on survivin was also conducted. Survivin is a member of the inhibitor of apoptosis family of proteins that protects tumours from programmed cell death following activation of intrinsic or extrinsic apoptotic pathways. Analysis of protein expression and phosphorylation was conducted by Western Blot. Apoptosis was quantitatively assessed by flow cytometry analysis and annexin V staining.

A concentration of lapatinib was used (100 nM) that by itself did not induce significant apoptosis in ErbB2 overexpressing breast cancer cells, in order to evaluate whether lapatinib would elicit synergistic anti-tumour activity when combined with anti-ErbB2 antibodies. Treating BT474 breast cancer cells with sub-lethal concentrations of lapatinib alone resulted in decreased protein expression of phosphorylated ErbB2, phosphorylated Akt, phosphorylated Erk1/2, and survivin, with an increase in tumour cell apoptosis of approximately 20%. pAb alone reduced total ErbB2 (100 to 200 µg/mL), reduced phosphorylated Erk1/2 and ErbB3 (100 µg/mL), and caused complete loss of phosphorylated Akt expression (100 µg/mL), although survivin protein remained unchanged and cell survival was less affected. Trastuzumab (10 µg/mL) caused less inhibition of phosphorylated ErbB2, phosphorylated Erk1/2, and survivin, whereas phosphorylated Akt was decreased to a similar extent; consequently cell survival was less affected than treatment with lapatinib alone. Combining lapatinib with either pAb or trastuzumab resulted in complete loss of survivin protein with a marked induction of tumour cell apoptosis (40% of cell population were positive for Annexin V). Down-regulation of survivin rather than inhibition of p-Erk1/2 and/or p-Akt correlated with induction of apoptosis.

Antibodies, especially polyclonal antisera such as pAb, reduced ErbB2 signalling by down-regulating ErbB2 protein expression through receptor endocytosis [Park, 1992; Maier, 1991], an activity not shared by lapatinib. The combination of lapatinib and anti-ErbB2 antibodies led to the complete inhibition of phosphorylated ErbB2.

- RH2006/00066/01 - Effects of lapatinib on phosphorylation, activity and expression of ErbB1, ErbB2, Akt and Erk1/2 and EGF

This study only examined the effect of the two agents in combination by their ability to inhibit phosphorylation of proteins in the pathway, and did not evaluate the combined effect on growth inhibition.

In BT474 cells incubated with 1 µM lapatinib for 24 hours, epidermal grow factor (EGF) (50 ng/mL) was unable to stimulate phosphorylation of Erk1/2 or Akt. Treating HN5 cells with 5 µM lapatinib inhibited baseline levels of phosphorylated ErbB1 and blocked the stimulatory effect of EGF on phosphorylation of ErbB1, Erk1 and Erk2. The effects of lapatinib (0.5 or 1 µM) were further compared to those of trastuzumab (10 µg/mL) on phosphorylation of Erk1/2 in both BT474 and HN5 cells following 72 hours exposure. The effect observed with trastuzumab was limited on levels of phosphorylated Erk1/2 compared with untreated controls in either cell line, while lapatinib inhibited phosphorylated Erk1/2 at either dose in both BT474 and HN5 cells.

In S1 cells (mammary epithelial cells which express high levels of phosphorylated erbB2), lapatinib caused dose dependent inhibition of ErbB2 tyrosine phosphorylation following incubation for 72 h: partial inhibition was seen at 0.5 µM and with complete inhibition at 2.5 µM. After incubation for 72 h, lapatinib inhibited activated phosphorylated Erk1/2 by more than 50% at 0.5 and 2.5 µM, with 100% inhibition at 5 µM. Total steady state Erk protein remained unchanged. The effects of lapatinib on cell survival were then assessed in exponentially growing S1 cells. Treatment with lapatinib for 72 h resulted in an increase in the percentage of apoptotic cells from 2% to 46% (23-fold).

In Hb4a cells (mammary epithelial line that expresses low levels of both erbB2 and EGFR), lapatinib (5 µM) reduced baseline phosphorylated ErbB1 levels and blocked the stimulatory effects of EGF on ErbB1 tyrosine phosphorylation. Similarly, lapatinib reduced the baseline amount of phosphorylated ErbB2 and Erk, effects not reversed by EGF. In Hb4a cells after 72h exposure to trastuzumab (10 µg/mL), there was relatively little change in baseline levels of phosphorylated ErbB2 or Erk levels, while total ErbB2 steady state protein was reduced.

Concurrent treatment with lapatinib in combination with trastuzumab did not reduce levels of phosphorylated ErbB2 or Erk below those observed following treatment with lapatinib alone.

In Hb4a cells, EGF (50 ng/mL) stimulated cell growth by 20% over vehicle treated controls, while treatment with lapatinib (2.5 µM) inhibited cell growth by 50%. EGF was unable to reverse lapatinib induced growth inhibition.

- 2011N127934_00 - Drug interactions with lapatinib in trastuzumab conditioned HER2 amplified breast cancer cell lines

This study was conducted to examine the preclinical efficacy of two commonly used chemotherapy combinations with trastuzumab in trastuzumab conditioned cell lines and compare the efficacy with that seen when using lapatinib instead of trastuzumab. The following drug combinations were tested in vitro using cell proliferation assays in five breast cancer cell lines (BT474, SKBR3, and SUM225, BT-TR and SK-TR, the latter two lines being trastuzumab-conditioned breast cancer cell lines): lapatinib and trastuzumab, lapatinib and gemcitabine, lapatinib and vinorelbine, trastuzumab and gemcitabine, trastuzumab and vinorelbine.

Trastuzumab responses by 3D assay were similar to those observed in 2D culture. Using a cut-off of less than 1.2 fold decrease in proliferation by 2D assay and less than 20% decrease in colony number by 3D assay, the SUM-225, were classified as resistant (R) to trastuzumab by both assays. Lapatinib inhibited the proliferation of each of the cell lines in a concentration dependent manner. All of the cell lines were responsive to lapatinib when grown in soft agar in the presence of the IC50 concentration of lapatinib as determined by 2D assay.

Models of acquired trastuzumab resistance were established by culturing the trastuzumab sensitive breast cancer cell lines in 10^5 µg/ml trastuzumab for nine months. Trastuzumab inhibited the proliferation of the parental BT474 cells by 5.00 fold compared to 1.16 fold for the BT-TR cells by 2D assay. Using a cut-off of less than 1.2 fold decrease in proliferation by 2D assay and less than 20% decrease in colony number by 3D assay, the SUM-225, were classified as resistant (R) to trastuzumab by both assays.

Full-length and p95HER2 protein levels (a truncated form of ErbB2 resistant to trastuzumab) were unchanged in the BT-TR cells. Significantly increased levels of phosphorylated ErbB2 were detected. The BT-TR cells were sensitive (IC50 = 77 nM) to lapatinib. Significantly increased levels of pAKT were also detected in the BT-TR cell line.

The role of receptor tyrosine kinase (RTK) activation in acquired trastuzumab resistance was also investigated. No significant difference in total or phosphorylated HER3 or IGF-1R was detected in the BT-TR cells relative to parental cells. However, phosphorylation of EGFR was significantly increased in the trastuzumab conditioned cells.

Multiple drug effect analysis was done using five HER2-overexpressing established human breast cancer cell lines to determine the nature of the interaction between lapatinib and trastuzumab (synergy, addition, or antagonism). The drug concentrations used for these experiments ranged between 0.039 and 5.0 µmol/L for lapatinib, 2.8 and 720 nM for trastuzumab, 0.8 and 200 nM for

gemcitabine, and 0.07 and 18 nM for vinorelbine and were below the reported peak plasma concentrations achievable in humans for all drugs. BT474 and SKBR3 cells showed synergistic drug interactions. Trastuzumab resistant cell lines BT-TR and SK-TR lines also showed synergistic drug interactions between lapatinib and trastuzumab. This effect was not seen it the SUM225 cells that were intrinsically resistant to trastuzumab.

2.2.3. Ecotoxicity/environmental risk assessment

No increased use of lapatinib is expected with this combination with trastuzumab which is to be administered to patients who would already be eligible for lapatinib at a dose lower than the dose currently approved for its use with capecitabine. Therefore, no need for further update of the initial environmental risk assessment (ERA) has been identified.

2.2.4. Discussion on non-clinical aspects

Overall, based on the *in vitro* studies described there was a possibility of a synergic effect between lapatinib and trastuzumab, or a possible benefit of adding lapatinib to trastuzumab therapy. The sites of action of lapatinib and trastuzumab were not coincident. While trastuzumab seemed to bind in a juxtamembrane region of the ErbB2 receptor not involved in receptor dimerization, which it inhibited, lapatinib binded ErbB2 in the ATP site and inhibited the tyrosine kinase activity located in the intracellular domains of ErbB2 and its co-receptor EGFR and the phosphorylation of both ErbB2 and EGFR were blocked. From a mechanistic point of view, it could therefore be justified to consider the association of lapatinib to trastuzumab to strengthen the ErbB2 blockade and cut the downstream cascade more efficiently than each of the molecules separately. However, since the true binding sites for trastuzumab and the mechanisms of trastuzumab resistance, as well as the different cross talk aspects of the ErbB2 domains to other cascades were not fully clarified, the plausibility might not reflect the reality in the complex environment of tumour cells. Thus, only the principle was supported by the results of *in vitro* studies in trastuzumab sensitive and trastuzumab resistant tumour cell lines.

In vitro studies to investigate the effect trastuzumab may have on the modulation of the CYP enzymes and transporters important to lapatinib metabolism have not been submitted.

No toxicity studies with the combination lapatinib and trastuzumab were submitted which was considered acceptable since the toxicities of both molecules are well known and did not suggest possibilities for potentiation.

The updated data submitted in this application did not lead to a significant increase in environmental exposure further to the use of lapatinib. The CHMP considered that the existing ERA for lapatinib adequately covered this application. Lapatinib should continue to be used according to the precautions currently stated in the SmPC in order to minimise any potential risks to the environment.

2.2.5. Conclusion on the non-clinical aspects

In conclusion, the non-clinical pharmacology studies submitted supported the proposed combination of lapatinib with trastuzumab.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. A routine GCP inspection was performed in three study sites with no critical findings.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Clinical pharmacology studies

Study Identifier / Reporting Status	**Type of study**	**Study objective (s)**	**Study design**	**Key inclusion criteria**	**No. of Subjects Gender M/F Mean Age (Range)**	**Treatment Details (Drug/Dose/Form/Route/Frequency /Duration**
EGF10023 Completed	Safety, tolerability, PK	Optimal tolerated dose, clinical activity	O, NR, DR, XO (PK)	Subjects with breast cancer over-expressing ErbB2	54 (0/54) 53y (30 – 80y)	Lapatinib: 750mg – 1500mg PO QD Trastuzumab IV 4mg/kg loading dose (90 min IV infusion) + 2mg/kg IV weekly (90 min IV infusion)
EGF105635 Completed	Safety, tolerability, PK	Optimal tolerated dose, clinical activity	O, NR, DR,	Subjects with breast cancer over-expressing ErbB2	6 (0/6)	Lapatinib: 750mg – 1000mg PO QD Trastuzumab IV 4mg/kg loading dose (90 min IV infusion) + 2mg/kg IV weekly (90 min IV infusion)

O = Open; SB = Single Blind; DB = Double Blind; UC = Uncontrolled; PLC = Placebo; AC = Active control; R = Random; NR = Non-random; PRL = Parallel; XO = Crossover; DR = Dose Rising; F – Female; M – Male.

Main clinical efficacy studies

Study Identifier /Reporting Status	**Study Design**	**Study Objective(s)**	**Diagnosis of Subjects**	**Total No. of Subjects**	**Treatment Details**
EGF104900 **Pivotal** Completed	Phase 3, randomised, two-arm, open label	Safety, efficacy, pharmaco-genetics	**Metastatic setting**. Subjects with advanced or metastatic breast cancer whose disease has progressed on a trastuzumab containing regimen	N=296 Lapatinib + Trastuzumab=148 Lapatinib alone=148	Lapatinib 1000 mg PO QD + trastuzumab 4 mg/kg IV load and 2 mg/kg IV weekly *vs.* Lapatinib 1500 mg PO QD
EGF106903 **Supportive** Ongoing	Phase 3, randomised, three-arm, open label	Efficacy, safety, biomarker	**Neoadjuvant setting**. Subjects with HER2/ErbB2 over-expressing and/or amplified primary breast cancer	N=455	Neoadjuvantly, for a total of 6 weeks: Lapatinib 1500 mg OD; *vs.* Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly, *vs.* Lapatinib 1000 mg OD with trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly. This is followed by

					combination with paclitaxel 80 mg/m^2 for 12 weeks followed by definitive surgery (lapatinib dose 750 mg/day in combination with trastuzumab). After surgery, patients will receive 3 courses of adjuvant chemotherapy with FEC, followed by the same targeted therapy as in the neoadjuvant setting to a total duration of the anti-HER2 therapy of 52 weeks. (lapatinib dose 1000 mg/day in combination with trastuzumab).
LPT109096 **Supportive** Ongoing	Phase 2, randomised, three-arm, open label	Efficacy safety, biomarker, pharmaco-genetics	**Neoadjuvant setting**. Subjects with invasive HER2 over-expressing breast cancer who have had no previous chemotherapy	N=109	Arm 1: Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly, *vs.* Arm 2: Lapatinib 1250 mg PO QD, *vs.* Arm 3: trastuzumab (given as on Arm 1) and lapatinib 750 mg PO QD during run-in and FEC therapy, then 1000 mg during the Paclitaxel therapy. Each arm will receive study drug treatment for 14 days, then study drug treatment + FEC75 for 12 weeks, then study drug treatment + paclitaxel for 12 weeks

2.3.2. Clinical pharmacology

2.3.2.1. Pharmacokinetics

Pharmacokinetic data for lapatinib were submitted and evaluated previously within the initial MAA, subsequent post-authorisation measures and variations. As part of the current application, the MAH submitted the results of two clinical studies EGF10023 and EGF105635 as listed in the above table.

Study EGF10023

Methods

This was a phase I, open-label study designed to determine the safety, tolerability, optimally tolerated regimen (OTR), and pharmacokinetics (PK) of lapatinib and trastuzumab in combination in patients with breast cancer whose tumours over expressed HER2.

Lapatinib was administered orally, once daily on a continuous basis starting with a dose of 1000 mg/day and trastuzumab 4 mg/kg IV loading dose (90-min IV infusion) with weekly doses of 2 mg/kg IV (90-min IV infusion). Planned doses of lapatinib were 750 mg/day to 1500 mg/day. Trastuzumab doses were not escalated or reduced but administered at the dose and schedule noted above. Cohorts of at least three subjects were enrolled at each dose level and monitored for toxicity. Dose escalation or reduction of lapatinib in subsequent cohorts was based on observed toxicity. The OTR was defined

as the highest dose of lapatinib that could be administered with trastuzumab at which no more than one of six subjects experienced dose-limiting toxicity (DLT).

During the first part of the study, the OTR was defined as 1000 mg lapatinib once daily with a standard regimen of trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly). Once the OTR was determined, up to 18 additional subjects were to be enrolled at this dose level to characterise the PK profiles of lapatinib and trastuzumab after administration of the three treatments: lapatinib alone, trastuzumab alone, and both in combination. Subjects were randomised into one of two treatment sequences. In sequence 1, subjects were administered lapatinib alone in treatment period 1 week 1, trastuzumab alone in week 2, and the combination of the two drugs in week 3. In sequence 2, subjects were administered lapatinib alone in treatment period 1 week 1, the combination of the two drugs in week 2, and trastuzumab alone in week 3. Pharmacokinetic sampling occurred over a 24-hour period on day 7 of each treatment week. The sampling period occurred on day 7 of lapatinib dosing or on the day of trastuzumab dosing.

Enzyme immunoassay (EIA) was used to determine trastuzumab, a humanized anti-human HER-2 receptor antibody, in human EDTA plasma. The calibration range was 5.00 to 100 µg/mL trastuzumab using a 50 µL aliquot of human plasma and the range of quantisation for the assay was 10.0 (LLQ) to 100 (HLQ) µg/mL. Human EDTA plasma samples were analysed for lapatinib using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The LLQ for lapatinib was 5 ng/mL using a 25 µL aliquot of human plasma with a HLQ of 5000 ng/mL.

Results

Dose-finding levels, dose-limiting toxicities and a summary of clinical activity results are presented under section 2.4.1, Dose-response study.

Pharmacokinetic results

In total, 24 evaluable subjects were included in the pharmacokinetic evaluation. Pharmacokinetic data were obtained from 24 subjects on lapatinib alone, 23 subjects on trastuzumab alone, and 22 subjects on both drugs in combination. The pharmacokinetic results for lapatinib and trastuzumab are shown in Table 1 and Table 2, respectively. The data indicated no effect of trastuzumab on lapatinib AUC(0-tau), Cmax, or Tmax. Also, lapatinib had no effect on trastuzumab AUC(0-24), Cmax, or Tmax.

Table 1 . Summary of lapatinib (1000 mg daily) pharmacokinetic parameters and statistical results with and without trastuzumab (2 mg/kg weekly)

Parameter (units)	Lapatinib alone* (n=24)	Lapatinib + Trastuzumab* (n=22)	Comparison** (n=22)
AUC(0-tau) (h•µg/L)	20.5 (15.6-26.9)	18.9 (14.4-24.7)	0.94 (0.81,1.1)
Cmax (µg/L)	1.60 (1.28-2.00)	1.50 (1.18-1.91)	0.96 (0.83,1.11)
tlag (h)	0.25 (0.00-0.5)	0.25 (0.00-2.25)	0.48 (-0.03,1.0)
tmax (h)	3.0 0 (0.00-12.00)	3.00 (0.00-8.00)	0.02 (-0.13,0.25)

* Geometric mean (95% confidence interval); tlag and tmax reported as median (range)

** Geometric least square mean ratio (90% confidence interval); tlag and tmax reported as median difference (90%CI)

Table 2. Summary of trastuzumab (2 mg/kg weekly) pharmacokinetic parameters and statistical results with and without co-administration of lapatinib (1000 mg daily)

Parameter (units)	Trastuzumab alone* (n=23)	Trastuzumab + Lapatinib* (n=22)	Comparison** (n=22)
AUC24 (h*µg/mL)	1306 (1185-1442)	1356 (1215-1514)	1.02 (0.99,1.06)
Cmax (µg/mL)	71.5 (64.7-79.1)	74.8 (66.4-84.2)	0.99 (0.79,1.07)
tmax (h)	2.50 (0.25-12.00)	2.25 (0.42-8.00)	0.00 (-1.00,1.09)

* Geometric mean (95% confidence interval); tmax reported as median (range)
** Geometric least square mean ratio (90% confidence interval); tmax reported as median difference (90%CI)

Study EGF105635

Methods

This phase I/II study evaluating lapatinib in combination with trastuzumab in patients with breast cancer previously treated with trastuzumab was conducted in Japanese subjects. The phase I part intended to confirm the recommended dose (as defined in study EGF10023), while the phase II part intended to confirm the safety and clinical response (tumour response rate) at the recommended dose. Female or male subjects with breast cancer tumours exhibiting ErbB2 over-expression who had received standard trastuzumab therapy for at least 6 weeks and had disease progression or relapse after the start of the last prior therapy were to be enrolled.

Results

Six subjects were enrolled. In the phase I part of the study, three female subjects each received daily 750 mg or 1000 mg oral lapatinib in combination with trastuzumab (4 mg/kg i.v. in the first week followed by 2 mg/kg i.v. weekly). The recommended dose of lapatinib in combination with trastuzumab was determined to be 1000 mg/day for Japanese subjects. The study was terminated prior to Phase II.

Pharmacokinetic results

Only a synopsis of the study report was submitted without detailed pharmacokinetic data. According to the study synopsis, pharmacokinetic results suggested that there was greater inter-individual variations in the plasma concentrations of lapatinib administered with trastuzumab than when lapatinib was administered alone (between-study comparison using data from the first-time use in human Japanese study). When lapatinib and trastuzumab were combined, AUC0-168hr and t½ for plasma trastuzumab concentrations were 4763.34 to 7137.24 hr•µg/mL and 79.06 to 112.24 hr, respectively.

2.3.2.2. Pharmacodynamics

No new pharmacodynamics data were provided within the application.

2.3.3. Discussion on clinical pharmacology

The data from Study EGF10023 indicated no pharmacokinetic interaction between lapatinib and trastuzumab. This is in line with what would have been expected based on mechanistic considerations, as lapatinib is a small molecule primarily metabolised via CYP3A4, and has been shown to be a weak CYP3A4/Pgp inhibitor, while trastuzumab is a monoclonal antibody not expected to be dependent on or to affect cytochrome P450.

Data from the combination study EGF105635 were very limited (n=6) and no detailed data were submitted. In addition, no conclusions can be drawn based on a between-study comparison. However, this is not considered of relevance for the current variation.

2.3.4. Conclusions on clinical pharmacology

Based on the available data, no pharmacokinetic interactions between lapatinib and trastuzumab have been observed. The pharmacokinetics of lapatinib is adequately reflected in the current product information.

2.3.5. Clinical efficacy

2.3.5.1. Dose response study

Study EGF10023

This was a phase I open-label study conducted to determine the safety, tolerability, optimally tolerated regimen (OTR), and pharmacokinetics of lapatinib and trastuzumab in combination. The method and pharmacokinetics results are presented under section 2.3.2, Pharmacokinetics. Fifty-four subjects with breast cancer whose tumours over-expressed HER2 were enrolled into three cohorts. Twenty-seven subjects were entered into the dose escalation and OTR expansion cohort and 24 subjects were entered into the pharmacokinetic cohort. Mean age was 53 years (range 30-80) and ethnicity was white in 85%. Out of 54 subjects, 50 had received prior trastuzumab therapy.

OTR endpoint

A dose regimen where ≤ one out of six (i.e. ≤ 16.7%) subjects experienced a dose-limiting toxicity (DLT) was defined as the OTR. DLT was defined as Grade 3 or 4 clinically significant non-haematological toxicity (excluding Grade 3 nausea), Grade 4 granulocytopenia lasting at least five days, thrombocytopenia (≤ 25,000/mm^3), or any Grade 2 non-haematological toxicity that persisted beyond the initial 4-week treatment period and was considered to be dose limiting by the investigator and medical monitor.

Table 3. Dose-finding levels for lapatinib in combination with standard dose trastuzumab, Study EGF10023

Total n in dose-escalating cohort: 27	**Lapatinib dose level -1 (750 mg/D)**	**Lapatinib dose level 0 (1000 mg/D)**	**Lapatinib dose level +1 (1250 mg/D)**	**Lapatinib dose level +2 (1500mg/D)**
N /level	3	11	10	3
DLT, n (%)	0 (0)	1 (9.1)	2 (20.0)	2 (66.7)

Table 4. Dose-limiting toxicities in the dose-escalating cohort of Study EGF10023

Subject	**Lapatinib dose level**	**DLT**	**Grade**	**Study day**
1	1000 mg/D	Weakness (asthenia) and fatigue	3	Day 3
2	1250 mg/D	Pain related to rash on scalp and face	3	Day 11
		Generalised rash and pruritus	3	Day 31
		Vaginal itching	3	Day 36
3	1250 mg/D	Diarrhoea	3	Day 15
4	1500mg/D	Fatigue	3	Day 15
5	1500mg/D	Diarrhoea, nausea and vomiting	3	Day 9

		Hypokalaemia	4	Day 12

The OTR was determined to be lapatinib 1000 mg/day plus trastuzumab 2 mg/kg administered weekly.

Table 5. Summary of Confirmed Clinical Activity, Study EGF10023

Cohort	Response	Starting Lapatinib Dose with Reductions (mg/day)	Response Duration (Days)	ER/PgR Status	Prior Therapy		
					Prior Trastuzumab ± Chemo	Chemo	Hormone
1[a]	CR	1500, 1000	331	-	1	2	0
1[a]	PR	750	155	-	2	2	0
1[a]	PR	1250, 1000	210	-	2	4	0
1[a]	PR	1250, 1000, 750	266	-	2	2	0
1[a]	PR	1000, 750	112	-	2	2	0
1[a]	PR	1000, 750	252	+	4	5	4
1[a]	PR	1000	84	+	6	4	1
3[e]	PR	1000	56	-	3	3	0

Note: Cohort 1= Dose-escalation phase of the study (total n= 27); Cohort 3 (PK) = sequence 1 was lapatinib/trastuzumab/both

Based on the DLT and clinical activity observed, 1000 mg lapatinib and standard dose trastuzumab was determined as the dose of Phase II studies.

The most common drug related AEs reported in this study were diarrhoea (81%), rash (54%), fatigue (52%), and nausea (50%). No drug-related deaths were reported. No clinically significant changes were observed for any laboratory value or vital sign.

2.3.5.2. Main studies

This application was supported by one phase III pivotal study in the metastatic setting (Study EGF104900) and two supportive studies in the neo-adjuvant setting: a phase III study (EGF106903) and a phase II study (LPT109096).

Pivotal study EGF104900

The original Clinical Study Report (CSR) dated 10 September 2008 was submitted with a Renewal procedure in 2009. This included efficacy results on the primary endpoint, progression free survival (PFS), and on secondary endpoints, overall survival (OS), overall tumour response rate (ORR), clinical benefit response rate (CBR), time to response (TTR), duration of response (DOR). An end-of-study abbreviated clinical study report (ACSR), dated 2 February 2012 was submitted with the present application. This contained updated OS results, and biomarker results.

Methods

Study participants

Eligible subjects were women ≥ 18 years with a confirmed diagnosis of HER2-positive MBC, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and left ventricular ejection fraction (LVEF) within institutional normal range. They were required to have received previous treatment with a taxane and an anthracycline, and had documented progression on at least one trastuzumab-containing regimen in the metastatic setting. The most recent treatment prior to study entry must have contained trastuzumab, either alone or in combination with other therapy in the metastatic

setting and subjects must have progressed while on this regimen. Subjects were required to have bone only disease or measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST).

The main inclusion and exclusion criteria are provided below:

Inclusion criteria

- Female of ≥18 years. Women of childbearing potential were to have a negative serum pregnancy test at screening and were to use an approved contraceptive method, if appropriate (for example, intrauterine device, birth control pills, or barrier device) beginning 2 weeks before the first dose of study treatment and for 28 days after the final dose of study treatment.

- Had histologically/cytologically confirmed MBC. If the disease was restricted to a solitary lesion, its neoplastic nature was confirmed by cytology or histology

- Had Stage IV breast cancer whereby their disease had progressed in either the adjuvant or metastatic setting. Prior therapies were to include, but were not limited to: Taxane-containing regimen for at least 4 cycles, or for 2 cycles provided disease progression occurred while on taxane; Anthracycline-containing regimen for at least 4 cycles, or for 2 cycles provided disease progression occurred while on anthracycline.

- Had documented progression following at least one trastuzumab plus cytotoxic chemotherapy or anti-hormonal regimen in the metastatic setting. The most recent treatment must have contained trastuzumab, either alone or in combination with other therapy in the metastatic setting, and subjects must have progressed while on this regimen. Progression was defined as either new lesions or a ≥20% increase in the sum of longest diameter (LD) on the progression radiologic scan.

- Had archived tumour tissue available for testing

- Had documented amplification of the ErbB2 gene by FISH or documented over-expression of the ErbB2 protein by IHC in primary or metastatic tumour tissue.

- Had an eligible lesion as follows: At least one measurable lesion(s) according to RECIST, or, Bone only disease.

- Had stable central nervous system (CNS) metastases defined as asymptomatic and not receiving systemic steroids and anticonvulsants for at least 1 month. Treatment with prophylactic anticonvulsants was permitted, unless listed within the prohibited medications.

- Radiotherapy if received within 2 weeks prior to initiation of study treatment to a limited area (e.g., palliative treatment for painful disease) other than the sole site of measurable disease was allowed. However, the subject must have completed treatment and recovered from all treatment related toxicities prior to administration of the first dose of study treatment.

- With the single exception of prior trastuzumab treatment, all prior chemotherapy, immunotherapy, biologic therapy, or surgery (except for minor surgical procedures) was discontinued at least 3 weeks prior to the first dose of study treatment. Subjects were to have recovered or stabilized sufficiently from treatment related toxicities prior to administration of the first dose of study treatment.

- Bisphosphonate therapy for bone metastases was allowed; however, treatment had to be initiated prior to the first dose of study treatment. Prophylactic use of bisphosphonates was permitted only for the treatment of osteoporosis.

- Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

- Was able to swallow and retain oral medication

- Had a cardiac ejection fraction within institutional range of normal as measured by echocardiogram (ECHO). Multigated acquisition (MUGA) scans were accepted in cases where an ECHO could not be performed or was inconclusive. The same modality used at baseline was to be used for repeat assessments throughout study.

- Had adequate hematologic, hepatic and renal functions as defined in the protocol.

- Subjects could continue anti-oestrogen therapy only if treatment was initiated at least 1 month prior to the first dose of study treatment. After randomization, no anti-hormonal therapy could be initiated.

Exclusion criteria

- Was a pregnant or lactating female.

- Had received prior therapy with an ErbB1 and/or ErbB2 inhibitor other than trastuzumab.

- Had malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. Subjects with ulcerative colitis were also to be excluded.

- Had a history of other malignancy. However, subjects who had been disease free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma were eligible.

- Had concurrent disease or a condition that made the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety.

- Had unresolved or unstable, serious toxicity from prior administration of another investigational drug and/or of prior cancer treatment.

- Had active or uncontrolled infection.

- Had dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.

- Had a known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure.

- Had a known history or clinical evidence of leptomeningeal carcinomatosis.

- Received concurrent cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy).

- Received concurrent treatment with an investigational agent or participation in another clinical trial.

- Had used an investigational drug within 3 weeks or 5 half-lives, whichever was longer, preceding the first dose of study treatment.

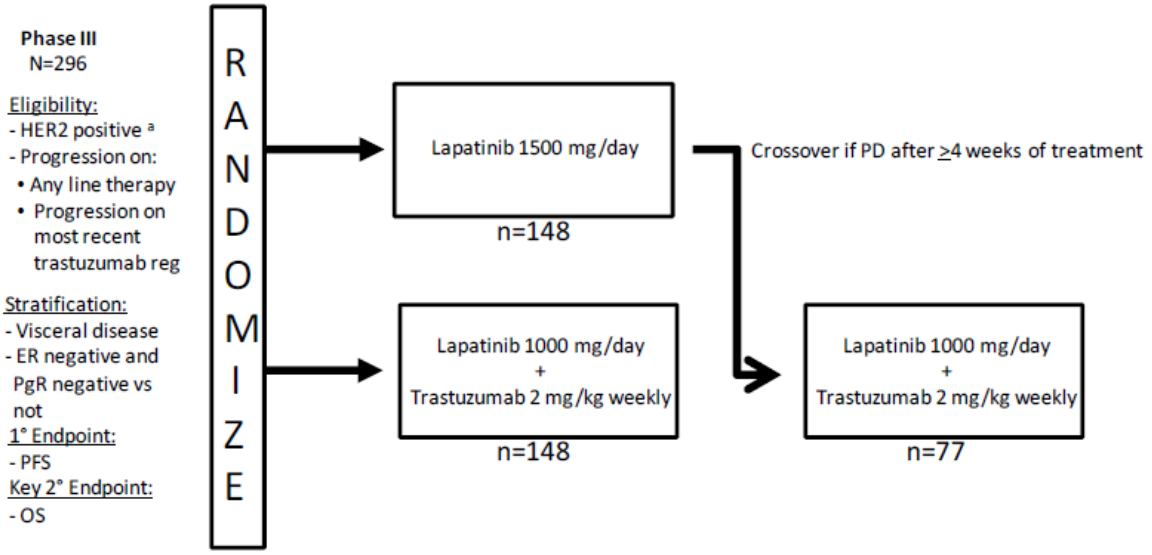
- Had known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trastuzumab or lapatinib or their excipients.

- Had current active hepatic or biliary disease (with the exception of subjects with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).

Treatments

The treatment arms are presented in Figure 1 and further detailed in Table 6.

Figure 1. Design of pivotal study EGF104900



a: FISH positive and IHC 3; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; OS = overall survival; PD = progressive disease; PgR = progesterone receptor; PFS = progression free survival.

Table 6. Treatment administered in study EGF104900

Drug	Dosage	Time for Administration
Combination arm		
Lapatinib	1000 mg (4 tablets)	Daily; approximately the same time of day each day, preferably either at least 1 hour before or 1 hour after breakfast
Trastuzumab loading dose[a]/Day 1	4 mg/kg IV infusion	Approximately 90 minutes on Day 1
Trastuzumab subsequent therapy	2 mg/kg IV infusion[b]	Approximately 30 minutes weekly
Monotherapy arm		
Lapatinib	1500 mg (6 tablets)	Daily; approximately the same time of day each day, preferably either at least 1 hour before or 1 hour after breakfast

Abbreviation: IV=Intravenous. a: If subjects were already receiving treatment with trastuzumab at the time of study entry then a loading dose did not need to be administered. b: Subjects remaining on study therapy at Week 108 and beyond may have received trastuzumab either at 2 mg/kg weekly or at 6 mg/kg at 3 week intervals (q3-weekly) according to the discretion of the investigator.

Trastuzumab was given in a weekly regimen, at least up until Week 108 (see also participant flow section).

Objectives

Primary objective

• Evaluate and compare the anti-tumour activity, in terms of progression-free survival (PFS), of trastuzumab plus lapatinib versus lapatinib monotherapy in subjects with ErbB2 gene amplified (HER2 over-expressing) MBC.

Secondary objectives

• Evaluate and compare the two treatment groups with respect to the following: overall survival (OS), tumour response rate (complete or partial), clinical benefit (complete response [CR], partial response [PR] or stable disease [SD] for at least 6 months), time to response and duration of response

• Determine the qualitative and quantitative toxicities associated with oral lapatinib administered daily in combination with trastuzumab versus lapatinib monotherapy, compare baseline and on-treatment serum concentrations of ErbB1 and ErbB2 ECDs, and potentially perform proteomic analysis to detect other shed tumour proteins, identify changes in the protein profile and correlate to treatment response

• Characterise the subject population by determination of intra-tumoural expression of ErbB1, ErbB2, and downstream biomarkers which may help elucidate the effects of lapatinib on the target and other proteins along relevant pathways in the tyrosine kinase pathway

• Evaluate quality of life (QOL) status within the study population and compare the impact on QOL between treatment groups

The pharmacogenomics (PGx) research objectives were to investigate the relationship between genetic variants and safety and/or tolerability of study treatments and the relationship between genetic variants and efficacy of study treatments if high variability in responses were observed.

Proteomic analyses were performed on plasma samples taken at specified visits to identify changes in the protein profile that were associated with response to study treatments.

RECIST guidelines were used to assess clinical activity and disease status. The investigator assessed responses and the independent reviewer confirmed responses were both reported.

Outcomes/endpoints

Primary endpoint

The primary efficacy analysis was based on PFS, defined as the time from randomisation until the first documented sign of disease progression or death due to any cause. The date of objective disease progression was defined as the date of radiological disease progression as assessed by the investigator, based on imaging data. If symptomatic progression was documented without radiological progression, the symptomatic date of progression was used.

Subjects whose disease did not progress or who received additional anticancer therapy (including combination therapy following crossover from monotherapy) prior to documented disease progression, were censored on the date of their last radiological assessment preceding the start of any additional anticancer therapy.

Secondary endpoints

- Overall survival (OS) was defined as the time from randomisation until death due to any cause. For subjects who did not die, time to death was censored at the time of last contact.

- Overall Tumour Response Rate (ORR) was defined as the percentage of subjects experiencing either a confirmed CR or confirmed PR. Subjects with an unknown or missing response were treated as non-responders (i.e., they were included in the denominator when calculating the percentage).

- Clinical Benefit Response Rate (CBR) was defined as the percentage of subjects with a confirmed CR or PR at any time or SD for at least 24 weeks. Subjects who withdrew from the study prior to completing 24 weeks were still counted in this analysis in the denominator.

- Time to Response (TTR) and Duration of Response (DOR): There were not enough subjects with a confirmed CR or confirmed PR to analyse these outcome measures using Kaplan-Meier curves as specified in the protocol.

- Time to Progression (TTP) was defined as the interval between the date of randomisation and the earlier of date of disease progression or death due to breast cancer. TTP was specified in the

protocol as a secondary endpoint. However, the endpoint is confounded by death due to other causes and is similar to PFS and therefore only PFS was examined.

- Quality of Life (QOL) was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT B) questionnaire (Version 4, 1997). The FACT B consists of the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire plus the Breast Cancer Subscale which complements the general scale with items specific to QOL in breast cancer. QOL was measured until subjects had disease progression. Most subjects had a preserved performance status at the start of the study, and were asymptomatic. Data were not captured following disease progression, where deterioration in QOL is to be expected.

Sample size

The sample size calculation was based on the assumption of median PFS of 8 weeks and 12 weeks in the monotherapy arm and the combination arm, respectively (i.e., a HR of 0.667).

A maximum of 192 subjects with disease progression were required. To achieve this number, an estimated total of 270 subjects were required.

Randomisation

Each subject was randomly assigned to a treatment arm stratified according to site of disease (visceral/non-visceral) and hormone receptor status. For all efficacy analyses, significance tests were stratified by site of disease (visceral/non-visceral) and hormone receptor status.

Blinding (masking)

Not applicable as treatments in this study were administered open-label.

Statistical methods

The primary population for efficacy analyses was the Intent-to-Treat (ITT) population, which included all subjects randomised to the study irrespective of whether or not study treatment was received and was according to the treatment to which they were randomised. PFS was summarised using Kaplan-Meier curves and compared between treatment arms using a stratified (see Randomisation) log-rank test. The Pike estimator of the treatment HR based on the log-rank test was provided, together with a 95% CI. Of the 296 subjects in the ITT Population, 5 subjects did not have hormone receptor status (estrogen receptor and/or progesterone receptor) verified in the case report form (CRF) data. Therefore the data for these subjects were excluded in any efficacy analyses adjusted for stratification factors. These analyses used the pre-defined stratified analyses described, but were based on the 'ITT Population with Strata' and were considered to be the primary analyses.

Supporting PFS analyses were provided based on the independent review assessments. Analyses on the Per Protocol (PP) Population and the Crossover Population were also performed.

The OS analysis was performed for both the ITT and Cross-Over populations. OS was summarised using Kaplan-Meier curves and compared between treatment arms using a stratified log-rank test. OS was summarised at the time of PFS analyses and when the OS data became mature (75% death events).

Exact 95% confidence intervals [CIs] for the overall tumour response rates in each arm were calculated. Non-stratified exact 95% CIs for the difference in overall tumour response rates were also

calculated. Overall tumour response rates were compared between treatment arms using stratified Fisher's exact tests. Zelen's test for homogeneity of the odds ratios across all strata were performed as a measure of validation.

Results

Participant flow

An overview of the participant flow is presented in Figure 1.

Among 296 randomised patients, 86% of patients completed the study (died, were lost to follow-up or received treatment through Week 108) as of the final data cut-off date (29 October 2010). Details for premature withdrawals (14%) and primary reason for discontinuation are presented in Table 7 and Table 8 respectively.

Table 7. Subject Accountability (ITT Population)

	Combination arm (N=148)	Monotherapy arm (N=148)	All Subjects (N=296)
Status, n (%)			
Completed study[a]	130 (88)	126 (85)	256 (86)
Prematurely withdrawn from study	18 (12)	22 (15)	40 (14)
Ongoing	0	0	0
Reason for withdrawal from study, n (%)			
Adverse event	0	0	0
Lost to follow-up	7 (5)	10 (7)	17 (6)
Protocol violation	0	0	0
Subject consent withdrawn	6 (4)	7 (5)	13 (4)
Sponsor closed the study follow up period[b]	2 (1)	1 (<1)	3 (1)
Death	1 (<1)	2 (1)	3 (1)
Investigator decision	0	1 (<1)	1 (<1)
Other	2 (1)	1 (<1)	3 (1)

a. 'Completed' was defined when a subject died, was lost to follow-up, or when another reason existed that prevented additional data collection. A subject who met the definition for completion may have been inadvertently captured under a withdrawal criterion (lost to follow-up or death).

b. Follow-up for survival was ceased by Protocol Amendment 3 once the OS data were considered mature.

Table 8. Primary Reason for Discontinuation from Treatment (Safety population[a])

	Combination therapy only (N=149)	Monotherapy arm (N=146)	
		Monotherapy only (N=69)	Monotherapy followed by crossover (N=77)
Status, n (%)			
Currently discontinued	149 (100)	69 (100)	77 (100)
On study treatment >48 weeks	3 (2)[b]	0[b]	2 (3)[b]
Currently ongoing	0	0	0
Reason for discontinuation from all study treatment, n (%)[b]			
Adverse event	16 (11)[c]	10 (14)[d]	5 (6)
Lost to follow-up	0	0	0
Protocol violation	0	0	0
Subject consent withdrawn	6 (4)	4 (6)	3 (4)
Sponsor closed the study follow up period[e]	0	1 (1)	0
Disease progression	119 (80)	52 (75)	63 (82)
Death	2 (1)	2 (3)	3 (4)
Other	3 (2)	0	1 (1)

a. This table is based on the Safety Population which is based on the treatment the subject actually received. Thus, this population differs from the ITT Population due to 1 subject who was randomized to the combination arm but did not receive

any study treatment. In addition, 2 subjects who were randomized to monotherapy treatment inadvertently received combination treatment.

b. 3 subjects in the combination arm and 2 subjects in the monotherapy crossover phase continued study treatment beyond 48 weeks. Since the eCRF was designed to record the reason for discontinuing study treatment only within 48 weeks of treatment, these 5 subjects do not have reasons entered for discontinuing study treatment. c. One subject had an AE that resulted in study treatment discontinuation (Table 31 of ACSR 'Adverse Events Leading to Discontinuation of Study Treatment Reported for More than One Subject in Either Arm regardless of Relationship to Study Medication'), however, the primary reason for study treatment discontinuation was listed by the investigator underlying disease progression.

d. One of the subjects initially listed by the investigator as discontinuing study treatment due to AEs was later identified as a case of disease progression. Therefore, one less subject is listed in the monotherapy arm in Table 31 of ACSR.

e. Follow-up for survival was ceased by Protocol Amendment 3 once the OS data were considered mature.

Recruitment

The EGF140900 study was conducted at 88 centres in 13 countries. The first subject enrolled in this study on 17 November 2005 and the last subject completed her final scheduled final visit on 29 October 2010. The data cut-off date for the primary endpoint, PFS, and secondary endpoints OS, ORR, CBR, TTR, DOR was 29 June 2007 (original CSR). All subjects were enrolled prior to that date.

The cut-off date for the OS analyses was 23 January 2009, which was when sufficient events had occurred to provide a mature dataset (end-of-study ACSR). For subject disposition and final cumulative safety analyses the cut-off date was 29 October 2010 (ACSR). The final database lock occurred on 5 May 2011.

Conduct of the study

The original protocol was dated 17 August 2005, and was amended three times.

Baseline data

Table 9. Demographic Characteristics (ITT Population), Study EGF104900

	Combination arm (N=148)	Monotherapy arm (N=148)	All Subjects (N=296)
Age (years)			
Median	52.0	51.0	51.0
Range	26 to 81	29 to 78	26 to 81
<65 years of age. N (%)	125 (84)	134 (91)	259 (88)
≥65 years of age, n (%)	23 (16)	14 (9)	37 (13)
<75 years of age, n (%)	142 (96)	145 (98)	287 (97)
≥75 years of age, n (%)	6 (4)	3 (2)	9 (3)
Race, n (%)			
White	137 (93)	140 (95)	277 (94)
African American/African Heritage	6 (4)	5 (3)	11 (4)
Asian	2 (1)	3 (2)	5 (2)
Central/South Asian Heritage	1 (<1)	1 (<1)	2 (<1)
Japanese/East Asian Heritage/ South East Asian Heritage	1 (<1)	2 (1)	3 (1)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Native Hawaiian or other Pacific Islander	2 (1)	0	2 (<1)

Based on data from cut-off date 29 June 2007.

Abbreviation: NOS=Not otherwise specified.

a. Time since first diagnosis was unknown for 2 subjects.

Table 10. Disease Characteristics at Screening (ITT Population), EGF104900

	Combination arm (N=148)	Monotherapy arm (N=148)	All Subjects (N=296)
Estrogen and Progesterone Receptor Status, n (%)			
Estrogen receptor positive or progesterone receptor positive	71 (48)	70 (47)	141 (48)
Estrogen receptor negative and progesterone receptor negative	75 (51)	75 (51)	150 (51)
Unknown[a]	2 (1)	3 (2)	5 (2)
HER2 Status IHC, n (%)			
0	3 (2)	6 (4)	9 (3)
1+	7 (5)	2 (1)	9 (3)
2+	24 (16)	20 (14)	44 (15)
3+	97 (66)	100 (68)	197 (67)
Unknown	12 (8)	13 (9)	25 (8)
Missing	5 (3)	7 (5)	12 (4)
HER2 Status FISH, n (%)			
Positive	131 (89)	122 (82)	253 (85)
Negative	0	5 (3)	5 (2)
Missing	17 (11)	21 (14)	38 (13)
Visceral or Nonvisceral Disease, n (%)			
Visceral (+/- non-visceral)	105 (71)	110 (74)	215 (73)
Nonvisceral only	43 (29)	38 (26)	81 (27)
Time from Last Trastuzumab, n (%)			
<1 Month	87 (59)	91 (61)	178 (60)
1 to 3 Months	52 (35)	47 (32)	99 (33)
>3 Months	6 (4)	7 (5)	13 (4)
Missing[b]	3 (2)	3 (2)	6 (2)

Based on data from cut-off date 29 June 2007.

a. Either estrogen receptor or progesterone receptor status was unknown for these subjects.

b. Disease progression was documented for these subjects but the time from the last trastuzumab dose to disease progression was not available.

Note: The table presented is based on available eCRF data; however, the efficacy analyses were stratified based on central laboratory and lesion data.

Baseline hormone receptor status, HER2 status by FISH and immunohistochemistry, visceral/non-visceral disease, and time from last trastuzumab (<1 month/1-3 months/>3 months) were well balanced between arms.

Histological grades at initial diagnosis are presented in the table below.

Table 11. Histological grade at initial diagnosis

Disease Characteristic	Dual Blockade Arm (N=148)	Lapatinib Arm (N=148)	All Subjects (N=296)
Primary Tumor Type, n (%)			
Breast Cancer	148 (100)	148 (100)	296 (100)
Histological Grade, n (%)			
Well differentiated	9 (6)	5 (3)	14 (5)
Moderately differentiated	33 (22)	30 (20)	63 (21)
Poorly differentiated	65 (44)	82 (55)	147 (50)
Undifferentiated	2 (1)	3 (2)	5 (2)
Grade could not be assessed	37 (25)	25 (17)	62 (21)
Unknown	2 (1)	3 (2)	5 (2)

Table 12. Metastatic disease sites present at baseline in more than 5% of subjects in either treatment arm (ITT Population)

	Combination arm (N=148)	Monotherapy arm (N=148)	All Subjects (N=296)
Elapsed Time Since Metastatic Diagnosis (years)			
n	132	124	256
Median	2.0	2.1	2.0
Range	0 to 10	0 to 10	0 to 10
Bone, n (%)			
Yes	79 (53)	79 (53)	158 (53)
No	69 (47)	69 (47)	138 (47)
Central Nervous System, n (%)			
Yes	15 (10)	19 (13)	34 (11)
No	121 (82)	110 (74)	231 (78)
Not Assessed	12 (8)	19 (13)	31 (10)
Chest wall, n (%)			
Yes	19 (13)	18 (12)	37 (13)
No	127 (86)	126 (85)	253 (85)
Not Assessed	2 (1)	4 (3)	6 (2)
Liver, n (%)			
Yes	81 (55)	81 (55)	162 (55)
No	66 (45)	67 (45)	133 (45)
Not Assessed	1 (<1)	0	1 (<1)
Lung, n (%)			
Yes	84 (57)	80 (54)	164 (55)
No	63 (43)	68 (46)	131 (44)
Not Assessed	1 (<1)	0	1 (<1)
Lymph nodes, n (%)			
Yes	64 (43)	71 (48)	135 (46)
No	82 (55)	77 (52)	159 (54)
Not Assessed	2 (1)	0	2 (<1)
Pleura, n (%)			
Yes	12 (8)	26 (18)	38 (13)
No	135 (91)	118 (80)	253 (85)
Not Assessed	1 (<1)	4 (3)	5 (2)
Skin, n (%)			
Yes	28 (19)	26 (18)	54 (18)
No	118 (80)	117 (79)	235 (79)
Not Assessed	2 (1)	5 (3)	7 (2)

Based on data from cut-off date 29 June 2007.

With the exception of pleural engagement, the metastasis sites were overall well balanced between arms and reflected the relatively late stage of disease.

Table 13. Prior Anticancer therapies of interest (ITT Population)

	Combination Arm (N=148)	Monotherapy Arm (N=148)	All Subjects (N=296)
Subjects with prior anti-cancer therapy, n (%)	**148 (100)**	**148 (100)**	**296 (100)**
Number of prior anti-cancer regimens, n (%)			
1-3	25 (17)	19 (13)	44 (15)
4-6	58 (39)	69 (47)	127 (43)
7-9	43 (29)	38 (26)	81 (27)
≥10	22 (15)	22 (15)	44 (15)
Median (range)	6 (2-18)	6 (1-17)	6 (1-18)
Subjects with prior hormonal therapy regimens, n (%)	**63 (43%)**	**63 (43%)**	**126 (43%)**
Number of prior hormonal containing regimens, n (%)			
1-3	47 (32)	51 (34)	98 (33)
4-6	14 (9)	12 (8)	26 (9)
≥7	2 (1)	0	2 (<1)
Subjects with prior chemotherapy containing regimens, n (%)	**148 (100)**	**148 (100)**	**296 (100)**
Number of prior chemotherapy containing regimens, n (%)			
1-3	44 (30)	43 (29)	87 (29)
4-6	70 (47)	78 (53)	148 (50)
7-9	27 (18)	22 (15)	49 (17)
≥10	7 (5)	5 (3)	12 (4)
Median (range)	4.5 (2-12)	4 (1-12)	4 (1-12)
Number of prior chemotherapies, Median (range)	7 (2-20)	6.5 (1-18)	7 (1-20)
Subjects with prior anthracycline therapy, n (%)	**148 (100)**	**148 (100)**	**296 (100)**
Subjects with prior trastuzumab therapy, n (%)	**148 (100)**	**148 (100)**	**296 (100)**
Number of prior trastuzumab containing regimens, n (%)			
1-3	82 (55)	77 (52)	159 (54)
4-6	50 (34)	54 (36)	104 (35)
≥7	16 (11)	17 (11)	33 (11)
Median (range)	3 (1-12)	3 (1-13)	3 (1-13)
Subjects with prior trastuzumab in adjuvant setting, n (%)	29 (20)	24 (16)	53 (18)
Number of prior trastuzumab in adjuvant regimens, n (%)			
1	25 (17)	13 (9)	38 (13)
2	2 (1)	8 (5)	10 (3)
3	1 (<1)	3 (2)	4 (1)
≥4	1 (<1)	0	1 (<1)
Subjects with prior metastatic trastuzumab containing regimens, n (%)	**140 (95)**	**141 (95)**	**281 (95)**
Number of prior metastatic trastuzumab regimens, n (%)			
1	26(18)	15 (10)	41 (14)
2	36 (24)	37 (25)	73 (25)
3	22 (15)	27 (18)	49 (17)
≥4	56 (38)	62 (42)	118 (40)
Median (range)	3 (0-12)	3 (0-13)	3 (0-13)

Based on data from cut-off date 29 June 2007.

Numbers analysed

The ITT population comprised 148 subjects in each treatment arm. One subject randomised in the combination arm did not receive any study treatment. In addition, 2 subjects who were randomised to monotherapy treatment inadvertently received combination therapy. This resulted in the safety population consisting of 149 subjects in the combination arm and 146 subjects in the monotherapy arm (**Table 14**).

Of the 296 subjects in the ITT Population, 5 subjects did not have hormone receptor status (estrogen receptor and/or progesterone receptor) verified in the eCRF data. Therefore the data for these subjects were excluded in the primary efficacy analyses that adjusted for stratification (ITT population with strata).

Table 14. Analysis populations, pivotal study EGF104900

	Number (%) of subjects		
	Combination arm	Monotherapy arm	All Subjects
ITT population	148 (100)	148 (100)	296 (100)
ITT population with strata	146 (99)	145 (98)	291 (98)
PP population	145 (98)	141 (95)	286 (97)
HER2 positive population A[a]	147 (>99)	146 (99)	293 (99)
HER2 positive population B[b]	145 (98)	140 (95)	285 (96)
Safety population	149 (101)	146 (99)	295 (>99)
Crossover population	0	77 (52)	77 (26)

Based on data from cut-off date 29 June 2007.

a. The HER2 positive population A included subjects with tumours that were FISH ≥2.0 or IHC 3+ per central or local laboratory assay evaluation. b. The HER2 positive population B included subjects with tumours that were FISH ≥2.0 or if FISH was missing then IHC 3+ per central or local laboratory assay evaluation. The HER positive populations A and B were to be analysed only if >5% of the ITT Population did not meet the HER2 positive eligibility criteria. Since greater than 95% of subjects in each treatment arm of the ITT population were ErbB2 positive the additional efficacy analyses for these populations defined in the analysis plan were not performed.

Outcomes and estimation

Primary endpoint - PFS

Investigator-evaluated PFS was the primary endpoint of the study.

Table 15. Investigator-Evaluated Progression-Free Survival (Study EGF104900, ITT Population with Strata [a])

	Dual Blockade Arm (N=148)	Lapatinib Arm (N=148)
Number of subjects, n (%)		
Evaluable subjects [a]	146 (100%)	145 (100%)
Progressed or died	127 (87)	128 (88)
Censored, follow-up ended	2 (1)	4 (3)
Censored, follow-up ongoing	17 (12)	13 (9)
Kaplan-Meier estimate (weeks)		
First quartile (95% CI)	5.1 (4.3, 6.7)	4.3 (4.1, 4.9)
Median (95% CI)	12.0 (8.1, 16.0)	8.1 (7.6, 9.0)
Third quartile (95% CI)	24.4 (17.6, 31.7)	13.4 (11.3, 17.1)
Hazard ratio estimate [b]	0.73	
95% CI	0.57, 0.93	
Log-rank p-value [c]	0.008	

Based on data from cut-off date 29 June 2007

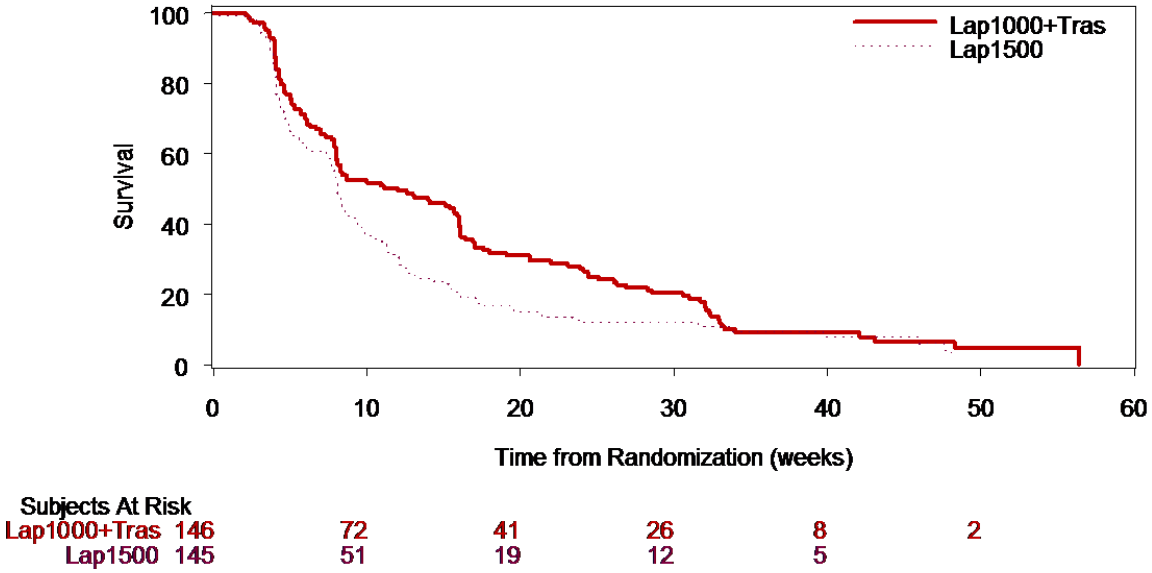
CI = confidence interval; ITT = intent-to-treat; N = number of subjects in the ITT population with strata

The number of evaluable subjects is less than the number of subjects in the ITT population because progesterone receptor status, which was required for stratification, was missing for 2 subjects in the dual blockade arm and 3 subjects in the lapatinib arm. This analysis population is therefore identified as "ITT population with strata".

A hazard ratio <1 indicates a lower risk with dual blockade therapy than with lapatinib alone.

P-value from stratified log-rank test, stratifying for presence of visceral/non-visceral disease and estrogen receptor/progesterone receptor status at baseline.

Figure 2. Kaplan-Meier Estimates of Investigator-Evaluated Progression-Free Survival (Study EGF104900, ITT Population with Strata)



Based on data from cut-off date 29 June 2007.

Table 16. Summary of PFS analyses and results

Analysis population and data set	ITT with strata Investigator assessed PFS		ITT with strata Independent review PFS		PP with strata Investigator assessed PFS		PP with strata Independent review PFS	
Treatment arm	Trast + lap	Lap mono	Trast + lap	Lap mono	Trast + lap	Lap mono	Trast + lap	Lap mono
Total n	146	145	146	145	143	139	143	139
Events, n (%)	127 (87)	128 (88)	83 (57)	79 (54)	125 (87)	123 (88)	82 (57)	74 (53)
Median PFS, weeks	12.0	8.1	16.4	11.1	12.6	8.1	16.4	11.4
Difference in medians, weeks	3.9		5.3		4.5		5.0	
HR (CI)	0.73 (0,57, 0.93)		0.71 (0.52, 0.98)		0.72 (0.56, 0.92)		0.71 (0.52, 0.99)	
p-value	0.008		0.027		0.006		0.030	

Data as of 29 June 2007.

Abbreviations (top-bottom): ITT = intention-to treat, PP = per protocol, PFS = progression-free survival, trast = trastuzumab, lap = lapatinib, mono = monotherapy, n = numbers, HR = hazard ratio, CI = confidence interval.

Secondary endpoints

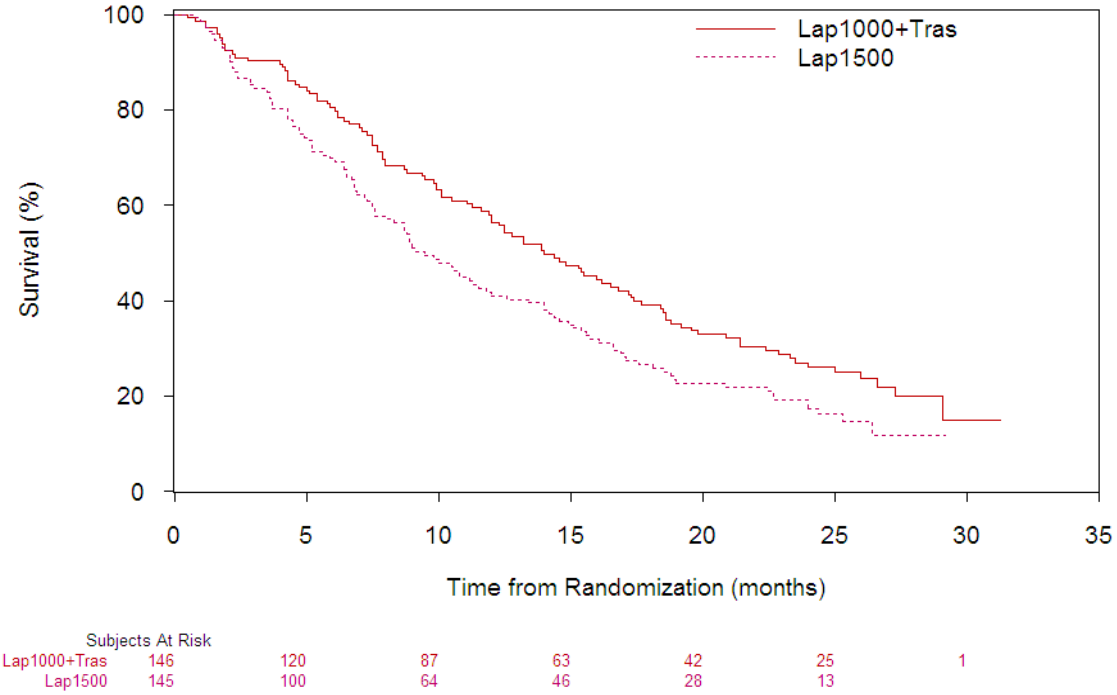
- ***Overall survival (OS)***

Table 17. Kaplan Meier Estimate of Overall Survival (ITT Population with Strata)

	Dual blockade arm (N=148)	Monotherapy arm (N=148)
Number of subjects, n (%)		
N	146	145
Died (event)	105 (72)	113 (78)
Censored, follow-up ended	11 (8)	15 (10)
Censored, follow-up ongoing	30 (21)	17 (12)
Kaplan-Meier estimate for OS, months [a]		
First quartile (95% CI)	7.3 (5.8, 8.8)	4.9 (3.7, 6.5)
Median (95% CI)	14.0 (11.9, 17.2)	9.5 (7.6, 12.0)
Third quartile (95% CI)	26.0 (19.8, NA)	18.8 (15.6, 24.0)
Hazard ratio		
Estimate (95% CI) [b]	0.74 (0.57, 0.97)	
Stratified log-rank p-value [c]	0.026	

Based on data from cut-off date 23 January 2009.
CI = confidence interval, ITT = intent-to-treat, NA = not applicable
a. Overall survival is defined as the time from the date of randomization until death due to any cause or to date of censor.
b. Pike estimate of the treatment hazard ratio, <1 indicates a lower risk with dual blockade treatment compared with monotherapy.
c. p-value from stratified log-rank test, stratifying for site of disease and ER/PR status at baseline.

Figure 3. Kaplan-Meier Estimates of Overall Survival (ITT Population with Strata)



Based on data from cut-off date 23 January 2009.

- ***Overall tumour response rate (ORR)***

Table 18. Investigator evaluated and independently evaluated best overall tumour response rate (by RECIST) (ITT Population)

	Investigator Evaluation		Independent Evaluation	
	Combination arm (N=148)	Monotherapy arm (N=148)	Combination arm (N=148)	Monotherapy arm (N=148)
Best Response, n (%)				
n[a]	146	145	146	145
Complete response (CR)	2 (1)	3 (2)	2 (1)	0
Partial response (PR)	13 (9)	7 (5)	7 (5)	4 (3)
Stable disease (SD)	57 (39)	40 (28)	65 (45)	56 (39)
Progressive disease (PD)	56 (38)	83 (57)	34 (23)	46 (32)
Unknown	18 (12)	12 (8)	38 (26)	39 (27)
Response rate (CR or PR)[b]				
Response rate, % (95% CI)	10.3 (5.9, 16.4)	6.9 (3.4, 12.3)	6.2 (2.9, 11.4)	2.8 (0.8, 6.9)
Difference in response rate (CR or PR)				
Difference, % (95% CI)	3.4 (-5.5, 14.0)		3.4 (-4.2, 13.1)	
Estimate of common odds ratio for tumor response				
Estimate (95% CI)	1.5 (0.6, 3.9)		2.2 (0.6 10.1)	
p value[c]	0.46		0.29	

a. The number of evaluable subjects is less than the number of subjects in the ITT population due to 5 subjects having missing progesterone receptor data, which was required for stratification.

b. Subjects with unknown or missing responses were treated as non-responders.

c. p-value from exact test that common odds ratio equals 1.

Response after cross-over

Based on both investigator and independent evaluation, 2.7% of subjects had a confirmed CR or PR after crossover to combination treatment.

ORR by investigator assessment was also analysed by the number of treatment regimens for metastatic disease (ad-hoc analysis). The response rate (CR+PR) in subjects with two or less prior regimens in the metastatic setting was 20.5% versus 11.8% in the combination and monotherapy arms, respectively (odds ratio: 1.9; 95% CI: 0.5, 9.6; p-value: 0.47); and 5.9% versus 5.4%, respectively, in subjects with more than two prior regimens in the metastatic setting (odds ratio: 1.0; 95% CI: 0.3, 4.0; p-value: 1.00).

- ***Clinical benefit response rate (CBR)***

Table 19. Investigator and Independently Evaluated Assessed Clinical Benefit response Rate (by RECIST) (ITT Population)

	Investigator Evaluation		Independent Evaluation	
	Combination arm (N=148)	Monotherapy arm (N=148)	Combination arm (N=148)	Monotherapy arm (N=148)
Clinical benefit response rate (CR or PR or SD ≥24 weeks)[a]				
Response rate, % (95% CI)	24.7 (17.9, 32.5)	12.4 (7.5, 18.9)	18.5 (12.6, 25.8)	9.0 (4.9, 14.8)
Difference in response rate				
Difference, % (95% CI)	12.2 (1.8, 23.5)		9.5 (-0.3, 20.6)	
Estimate of common odds ratio for clinical benefit				
Estimate (95% CI)	2.2 (1.2, 4.5)		2.2 (1.0, 4.9)	
p-value[b]	0.01		0.04	

a. Subjects with unknown or missing responses were treated as non-responders.

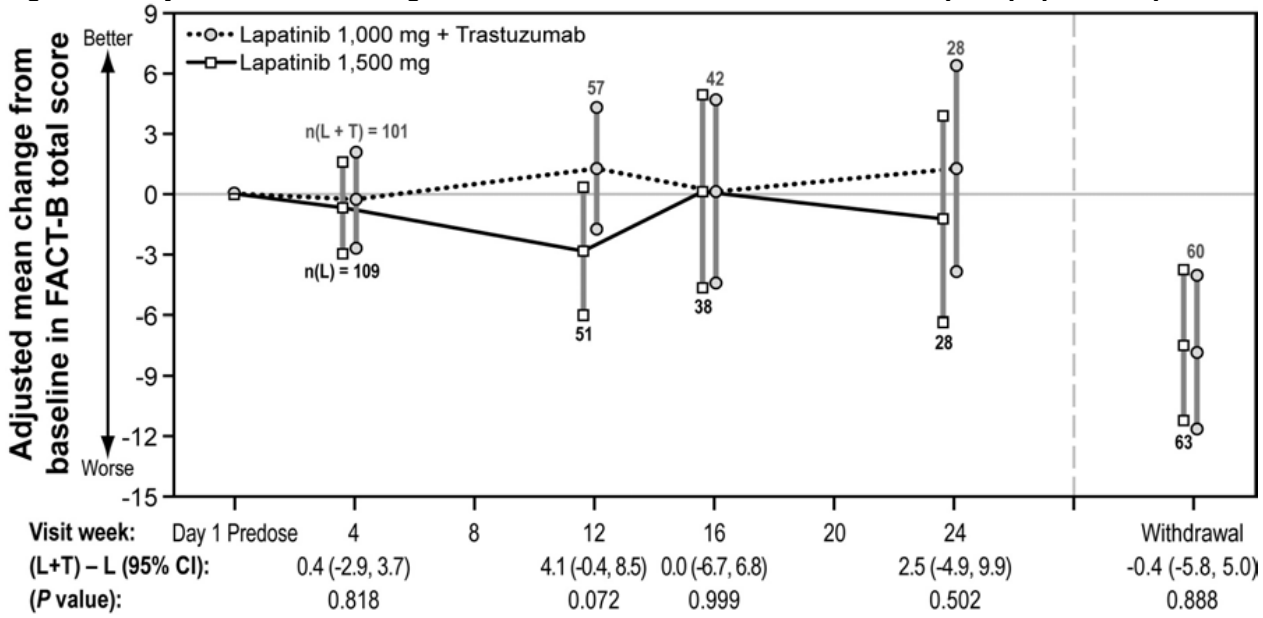
b. p-value from exact test that common odds ratio equals 1.

The CBR (CR+PR+ SD> 6 months) was doubled in the combination arm (24.7%) compared with lapatinib monotherapy (12.4%).

- ***Quality of Life (QoL)***

Of those patients who were randomised, approximately 95% in each arm completed a baseline QOL questionnaire. Because QOL assessments were stopped at treatment termination or disease progression, few subjects were on study and completed the questionnaire after week 24. Hence only results up to week 24 are summarised based on the data cut-off of 29 June 2007.

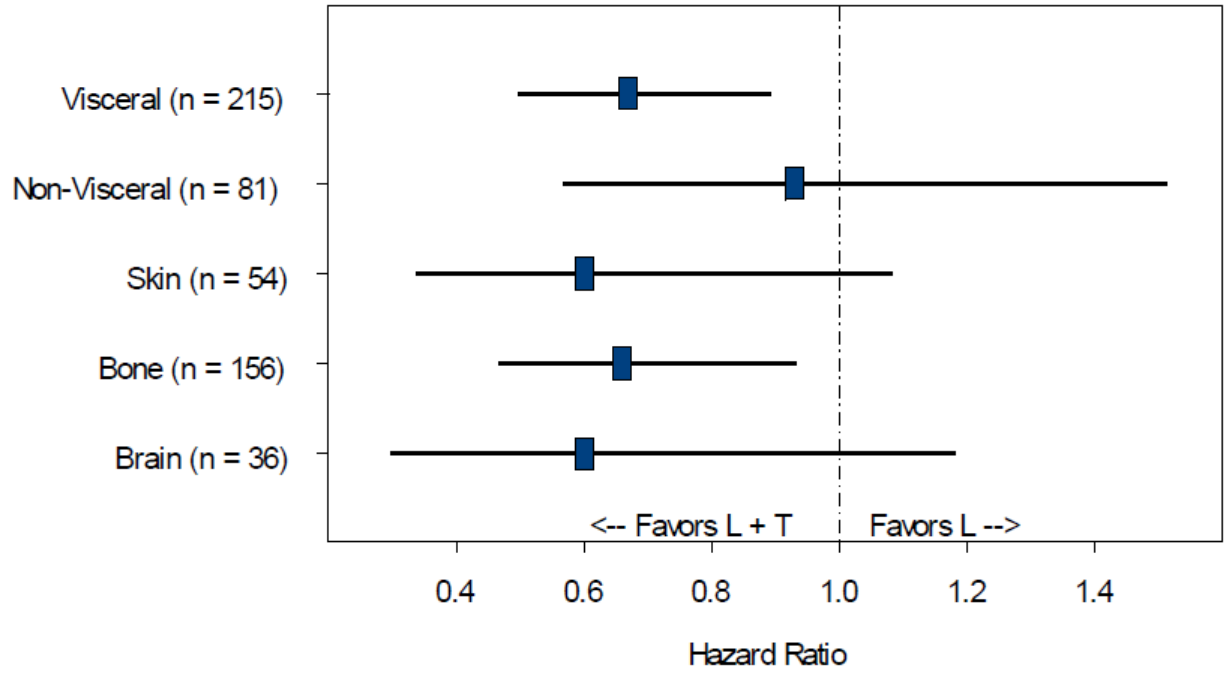
Figure 4. Adjusted Mean Change from Baseline in FACT-B Total Score (ITT population)



Ancillary analyses

Important metastatic sites

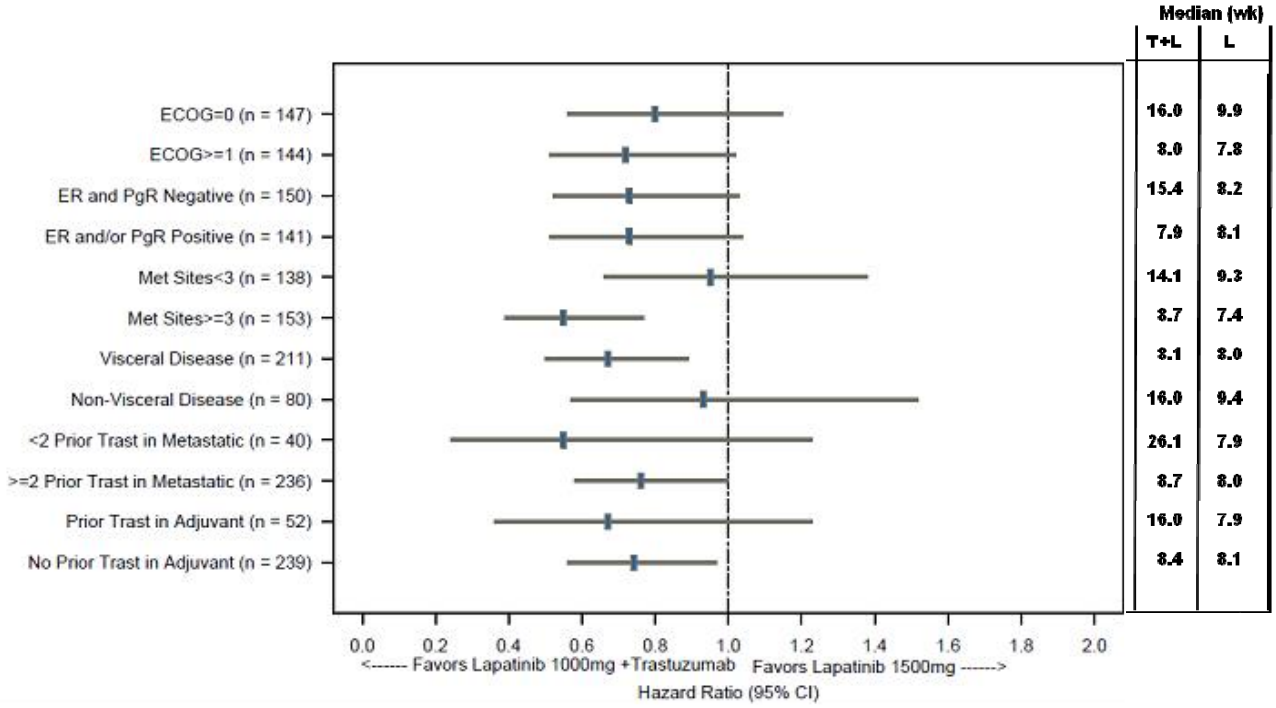
Figure 5. Summary of hazard ratios and 95% confidence intervals for investigator assessed Progression Free Survival subgroup analyses



Hazard Ratios Based on Pike Estimator. Stratified Hazard Ratio used for Bone Disease Subgroup.

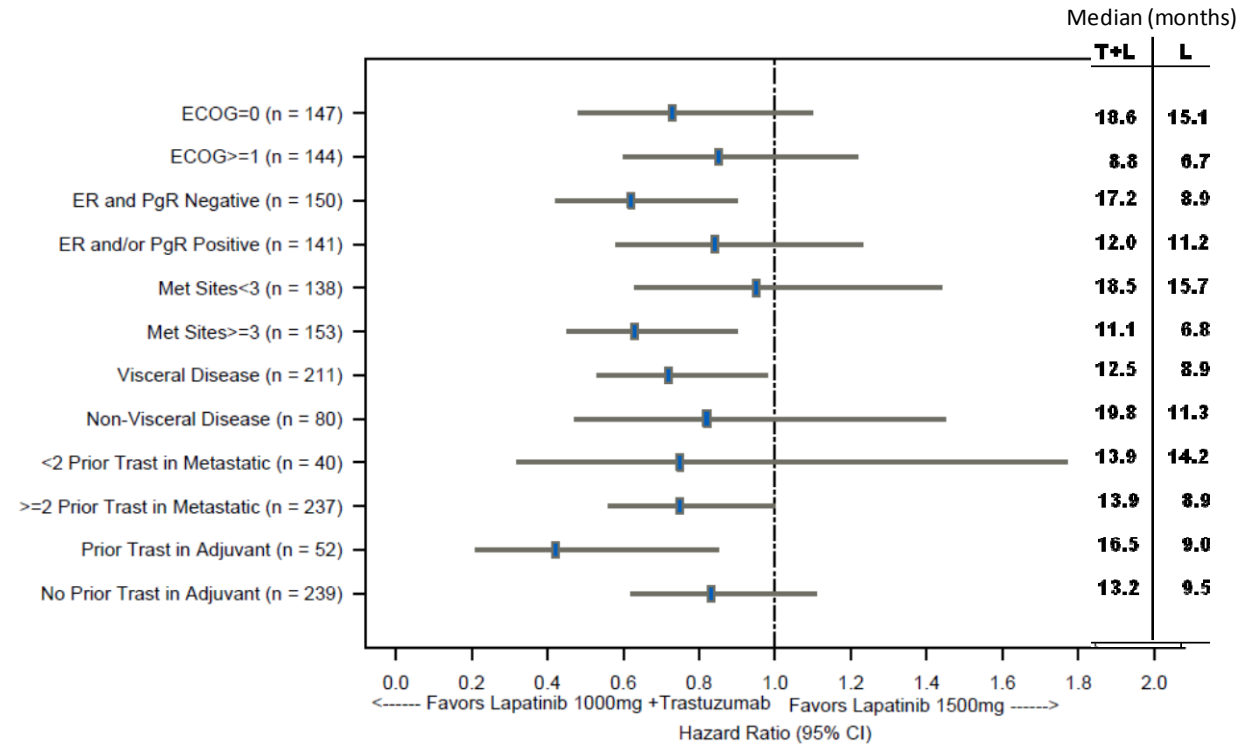
Major prognostic subgroups

Figure 6. Forest plot of hazard ratio (95% CI) and medians for investigator-assessed Progression Free Survival



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; PgR = progesterone receptor; Met = metastatic, ITT = intent to treat; Trast = trastuzumab

Figure 7. Forest plot of hazard ratio (95% CI) for Overall Survival



Data as of 23 January 2009

A stepwise Cox proportional hazard analysis was performed to identify independent factors influencing OS. Significant factors in the final model that positively influenced OS were ECOG performance status of 0, lack of visceral disease, <3 metastatic sites, and less time from initial diagnosis until randomisation. The adjusted HR for treatment of 0.71 (95% CI: 0.54, 0.93; p=0.0116) retained significance and represented a 29% reduction in the risk of death for subjects in the dual blockade arm compared with subjects in the lapatinib arm.

Post-study chemotherapies

Data on post-study therapies received following EGF104900 are summarised in the table below.

Table 20. Number of post-study chemotherapies (Intent-to-Treat population)

	Lapatinib 1000mg + Trastuzumab (N=148)	Lapatinib 1500mg (N=148)
Number of Subjects with Post Chemotherapy		
n	95	71
Median Number of Post Chemotherapies		
Median	2.0	2.0
Number of Post Chemotherapies		
1	34 (36%)	26 (37%)
2	22 (23%)	17 (24%)
3	16 (17%)	15 (21%)
>=4	23 (24%)	13 (18%)

While more subjects in the dual blockade arm received post-study chemotherapies, the numbers of post-study chemotherapies were well balanced between the arms with a median of two.

Table 21. EGF104900: Subjects receiving post-progression therapy with trastuzumab and lapatinib

	Number (%) of subjects		
	Dual Blockade Arm (N=148)	**Lapatinib Arm (N=148)**	**All Subjects (N=296)**
Original Analysis Excluding Cross Over Therapy[a] n (%)			
Number of Subjects who received Cross-over Therapy Prior to Entering Follow Up	NA	77 (52)	77 (26)
Any Therapy	101 (68)	76 (51)	177 (60)
Any HER2-Targeted Agent	71 (70)	54 (71)	125 (71)
Trastuzumab	48 (48)	47 (62)	95 (54)
Lapatinib	20 (20)	17 (22)	37 (21)
New Analysis Including Cross Over Therapy[b] n (%)			
Any Therapy	101 (68)	110 (74)	211 (71)
Any HER2-Targeted Agent	71 (70)	100 (91)	171 (81)
Trastuzumab	48 (48)	99 (90)	147 (70)
Lapatinib	20 (20)	77 (70)	97 (46)

a. Data as of 23 Jan2009

b. Data as of 23 Jan 2009

N/A Not applicable

As requested by the CHMP, the next-line therapies were further assessed. In EGF104900, the type, name and start date of post study treatment agents were captured and are summarised in the table below, to determine whether the type and line of therapy administered after completion of study medication could have influenced the study outcomes (Table 22). The duration of post-study therapies is also presented in Table 23.

Table 22. EGF104900: First next line therapy (ITT Population)

Anti-Cancer Therapy	Dual Blockade Arm N=148	Lapatinib Arm N=148	Lapatinib Arm	
			Non-crossover N=71	Crossover N=77
Number of subjects in follow-up, n (%)	**122 (82)**	**100 (68)**	**41 (58)**	**59 (77)**
Any Therapy [a]	**101 (68)**	**76 (51)**	**33 (46)**	**43 (56)**
Targeted agents	53 (52)	41 (54)	17 (52)	24 (56)
Trastuzumab	37 (37)	35 (46)	15 (45)	20 (47)
Lapatinib	5 (5)	6 (8)	1 (3)	5 (12)
Bevacizumab	12 (12)	3 (4)	3 (9)	0
Sunitinib Malate	0	1 (1)	0	1 (2)
Any chemotherapy	77 (52)	59 (40)	26 (37)	33 (43)
Anti-metabolites	39 (39)	28 (37)	11 (33)	17 (40)
Taxanes	17 (17)	17 (22)	9 (27)	8 (19)
Alkylating agents	11 (11)	13 (17)	7 (21)	6 (14)
Vinca alkaloids	12 (12)	5 (7)	0	5 (12)
Anthracyclines	7 (7)	5 (7)	2 (6)	3 (7)
Plant Alkaloid/Topo II Inhibitors	2 (2)	1 (1)	1 (3)	0
Topoisomerase I inhibitors	1 (<1)	0	0	0
Pemetrexed[b]	1 (<)	0	0	0
Hormonal	4 (4)	4 (5)	0	4 (9)
Bisphosphonates	1 (<1)	0	0	0
Other[c]	10 (10)	3 (4)	2 (6)	1 (2)

a. Does not include cross-over therapy
b. Pemetrexed was included in the "Other" category and not presented in EGF104900 ACSR Table 21; as such it was presented separately here
c. Other denotes all anti-cancer therapies not previously described in the EGF104900 ACSR Table 21 and includes calcium carbonate, neratinib, dasatinib, erlotinib, LBH-589, MK-0646, MKC-1, sirolimus, sorafenib, an investigational drug (NOS) and an ambiguous medication. All other medications were given to one or fewer subjects in each cohort, except for neratinib, which was given to 2 subjects in the dual blockade cohort.

Table 23. EGF104900: Duration of post study anti-cancer therapies

Duration of Post-Study Anti-Cancer Therapy (months)	Dual Blockade Therapy N=148	Lapatinib Monotherapy N=148
Line 1		
n	102	80
Median (Range)	5.7 (1-28)	4.3 (1-23)
Line 2		
n	67	47
Median (Range)	3.8 (0-13)	2.9 (0-14)

A post-hoc analysis investigating the effect of post-study therapies on OS results was performed. Post-study therapies comprised treatments administered from the time of discontinuation of all study therapy. Post-study therapies did not include dual blockade treatment received by the 77 subjects (52%) in the monotherapy arm who crossed over upon disease progression. Subsequent therapies for these subjects were captured following discontinuation of combination therapy.

Table 24. Kaplan Meier estimate of Overall Survival in subjects who received and did not receive post-study therapies (ITT population with strata)

	Subjects with Any Post-Study Treatment		Subjects with No Recorded Post-Study Treatment	
	Dual blockade arm	Lapatinib arm	Dual blockade arm	Lapatinib arm
Number of subjects, n (%)				
n	101	76	45	69
Died (event)	71 (70)	60 (79)	34 (76)	53 (77)
Censored, follow-up ended	4 (4)	4 (5)	7 (16)	11 (16)
Censored, follow-up ongoing	26 (26)	12 (16)	4 (9)	5 (7)
Kaplan-Meier estimate for OS, months				
First quartile	11.6	9.3	1.9	2.3
(95% CI)	(9.5, 13.9)	(8.3, 11.3)	(1.7, 4.6)	(2.0, 3.6)
Median	17.7	15.5	6.1	4.7
(95% CI)	(15.4, 20.9)	(13.4, 18.1)	(4.3, 7.9)	(3.7, 6.4)
Third quartile	27.3	24.0	9.4	7.5
(95% CI)	(23.3, NA)	(18.8, 26.4)	(7.3, NA)	(6.4, 12.0)
Hazard ratio				
Estimate (95% CI)	0.83 (0.59, 1.18)		0.72 (0.47, 1.10)	

CI = confidence interval; ITT – intent-to-treat; N = number of subjects; NA = not applicable; OS = overall survival

Types of PFS Events

Results of analyses of the types of PFS events in study EGF104900 are presented below.

Table 25. EGF104900: Summary of investigator-assessed progression events (ITT Population)

Investigator Evaluation	Dual Blockade Arm (N=148)	Lapatinib Arm (N=148)
Total number of PFS events	127	128
Radiological Progression, n (%)[a]	106 (83)	112 (88)
Symptomatic Progression, n (%)[a]	15 (12)	12 (9)
Death, n (%)[a]	6 (5)	4 (3)

PFS = progression-free survival
a Expressed as percentage of total number of PFS events

The reasons and sites for disease progression in EGF104900 are summarised in Table 27 and 28.

Table 26. EGF104900: Summary of reasons for progressive disease (ITT population)

Progressive Disease Reason	Lapatinib+Trastuzumab N=146 n (%)	Lapatinib N=145 n (%)
PFS Events	127	128
New Lesion Only	26 (18)	18 (12)
Progression in Existing Lesion Only	49 (34)	46 (32)
New Lesion and Progression in Existing Lesion	31 (21)	48 (33)
Death Only	6 (4)	4 (3)

Abbreviations: ITT=intent to treat; PFS=progression free survival

Table 27. EGF104900: Summary of sites of disease progression (ITT population)

Site of Progression	Lapatinib+Trastuzumab N=148 n (%)	Lapatinib N=148 n (%)
Visceral	89 (60)	99 (67)
Non-Visceral	19 (13)	19 (13)
Not Applicable	14 (9)	8 (5)

Non-visceral disease was defined as skin only, bone only, chest wall only, abdominal wall only or lymph node only. Visceral includes visceral only or visceral and non-visceral.

Tumour Histological Grade

An exploratory analysis was also performed to determine whether histological grade at initial diagnosis had any implication on progression-free survival (PFS) and overall survival (OS).

Table 28. EGF104900: Investigator-Assessed PFS and OS by Histological Grade at Initial Diagnosis (ITT Population)

	Poorly Differentiated or Undifferentiated		Moderately Differentiated or Well Differentiated	
	Dual Blockade Arm (N=67)	Lapatinib Arm (N=85)	Dual Blockade Arm (N=42)	Lapatinib Arm (N=35)
Investigator Assessed PFS [a]				
Progressed or Died, n (%)	56 (84)	77 (91)	39 (93)	28 (80)
Median, weeks	13.0	7.5	12.1	9.9
Hazard ratio (95%CI)	0.58 (0.41, 0.82)		0.83 (0.51, 1.36)	
Overall Survival [b]				
Died, n (%)	51 (76)	69 (81)	31 (74)	24 (69)
Median, months	12.5	8.8	14.6	14.0
Hazard ratio (95%CI)	0.70 (0.49, 1.01)		1.04 (0.61, 1.78)	

1. CI, confidence interval; PFS, progression-free survival
2. a. Based on clinical cut off 29 June 2007
3. b. Based on clinical cut off 23 January 2009

In order to understand whether a difference in benefit in histological subgroups is observed in other studies, histological subgroups were also evaluated for pCR in the neoadjuvant supportive study EGF106903 (NeoALTTO) (see also section 'Supportive studies').

Table 29. EGF106903: pCR in histological grade subgroups (ITT population)

	Lapatinib + Chemotherapy	Trastuzumab + Chemotherapy	Dual Blockade + Chemotherapy
Poorly or Undifferentiated			
N	73	68	64
pCR, % (exact 95% CI)	30.1 (19.9, 42.0)	29.4 (19.0, 41.7)	59.4 (46.4, 71.5)
Difference vs T arm, % (exact 97.5% CI)	0.73 (-18.1, 19.6)	N/A	30.0 (10.4, 47.7)
Well or Moderately Differentiated			
N	58	58	68
pCR, % (exact 95% CI)	15.5 (7.4, 27.4)	29.3 (18.1, 42.7)	42.7 (30.7, 55.2)
Difference vs T arm, % (exact 97.5% CI)	-13.8 (-34.5, 7.9)	N/A	13.3 (-6.6, 32.6)

Biomarker results

Serum HER2 extracellular domain (ECD) concentration

Baseline serum HER2 ECD concentration levels (collected prior to any study treatment) were available for 94% of subjects (279/296). Subjects were grouped according to whether HER2 ECD levels were elevated (>15 ng/mL) or at or below the reference normal value of 15 ng/mL [Carney, 2003] and evaluated for treatment outcome effects on PFS, ORR and CBR. At screening, the majority of subjects in the ITT population had HER2 ECD levels >15 ng/mL (60%).

Table 30. PFS Analysis by Baseline HER2 ECD levels (ITT Population)

	Combination arm (N=148)	Monotherapy arm (N=148)
Baseline HER2 ECD levels 15 ng/mL or lower, n (%)	47 (32)	52 (35)
Kaplan-Meier estimate for PFS, weeks		
Median (95% CI)	10.0 (7.9, 15.7)	8.0 (4.9, 11.9)
Hazard ratio estimate (95% CI)	0.93 (0.60, 1.42)	
Log-rank p-value	0.7161	
Baseline HER2 ECD levels greater than 15 ng/mL, n (%)	92 (62)	88 (59)
Kaplan-Meier estimate for PFS, weeks		
Median (95% CI)	15.9 (8.3, 17.6)	8.3 (7.7, 9.4)
Hazard ratio estimate (95% CI)	0.55 (0.40, 0.76)	
Log-rank p-value	<0.0001	

Based on data from cut-off date 29 June 2007.
Abbreviation: CI =Confidence interval; ECD=extracellular domain; PFS=progression free survival

At Week 4, there was a mean increase in HER2 ECD of 12% (standard deviation: 63%; range: -91% to 417%) in the combination arm, whereas a mean increase in HER2 ECD of 88% (standard deviation: 161%; range: -73% to 913%) was observed in the monotherapy arm.

Gene Expression Analysis

Archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue (collected prior to any study treatment) of sufficient quantity required for conducting the gene expression analysis was available for 156 subjects. Gene expression results were available for 68 subjects in the monotherapy arm and 65 subjects in the combination arm. Reasons for missing data were insufficient quantity of tumour tissue, poor quantity RNA or poor quality RNA. In analyses to identify differentially expressed genes between the treatment arms, no genes met the false discovery rate (FDR) significance threshold of ≤0.05, therefore the treatment arms were combined for further analyses. The results showed that high HER2 expression levels and low MMP7 expression levels were significantly associated with longer PFS in the combined population; there were no genes significantly associated with OS (FDR adjusted p-value >0.05).

Hormone Receptor Status

Table 31. EGF104900: Summary of PFS and OS – subgroup analysis by HR status

Study	Median PFS (95% CI)		Median OS (95% CI)	
	HR-negative	HR-positive	HR-negative	HR-positive
EGF104900				
Lapatinib + Trastuzumab	15.4 wks (8.4-16.9)	7.9 wks (6.3-15.7)	17.2 mos (13.9-19.2)	12.0 mos (9.4-15.4)
Lapatinib	8.2 wks (7.4, 9.3)	8.1 wks (6.1-9.9)	8.9 mos (6.7-11.8)	11.2 mos (8.0-15.4)
Hazard Ratio (95% CI)	0.73 (0.52-1.03)	0.73 (0.51-1.04)	0.62 (0.42-0.90)	0.84 (0.58-1.23)

Figure 8. EGF104900: Overall survival data - subgroup analysis by HR status Plot A HR Positive, Plot B HR Negative

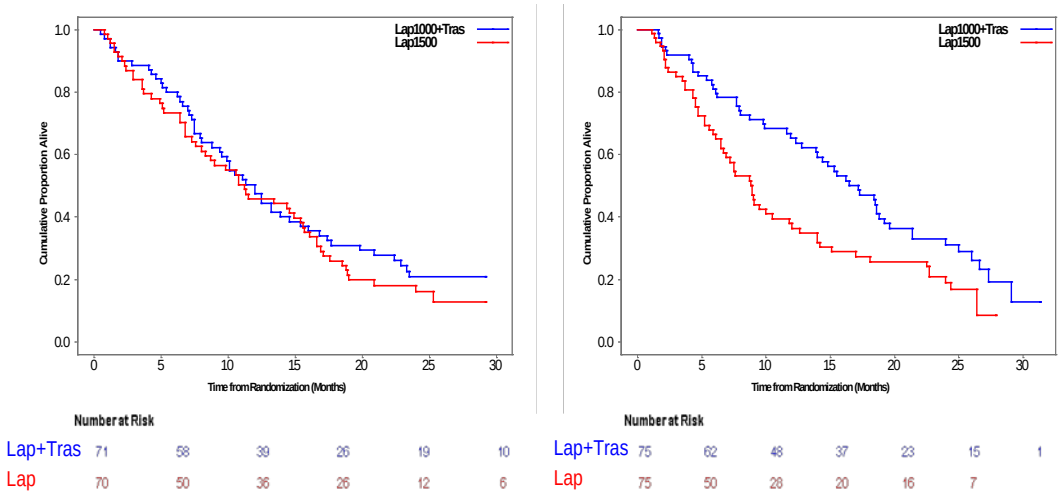


Table 32. EGF104900: Summary of ORR - subgroup analysis by HR status

Study	Hormone Receptor-Negative		Hormone Receptor-Positive	
	N	ORR %	N	ORR %
Controlled Metastatic Studies				
EGF104900				
Lapatinib + Trastuzumab	75	15 (7.6-24.7)	71	6 (1.6-13.8)
Lapatinib	75	8 (3.0-16.6)	70	6 (1.6-14.0)

HR subgroup analyses were also performed for pCR on the NeoALTTO study (Table 34) (see also section 'Supportive studies').

Table 33. EGF106903: pCR in hormone receptor subgroups (ITT population)

	Lapatinib + Chemotherapy	Trastuzumab + Chemotherapy	Dual Blockade + Chemotherapy
pCR [a]			
N	74	74	75
HR Negative Subgroup, % (95% CI)	33.8 (23.2, 45.7)	36.5 (25.6, 48.5)	61.3 (49.4, 72.4)
N	80	75	77
HR Positive Subgroup, % (95% CI)	16.3 (9.0, 26.2)	22.7 (13.8, 33.8)	41.6 (30.4, 53.4)
Loco-regional pCR [b]			
N	72	73	74
HR Negative Subgroup, % (95% CI)	26.4 (16.7, 38.1)	37.0 (26.0, 49.1)	56.8 (44.7, 68.2)
N	78	72	71
HR Positive Subgroup, % (95% CI)	14.1 (7.3, 23.8)	18.1 (10.0, 28.9)	36.6 (25.5, 48.9)

a. pCR was defined as no invasive cancer in the breast or only non-invasive in situ cancer in the breast.
b. Loco-regional pCR was defined as no invasive cancer in the breast (or only non-invasive in situ cancer in the breast specimen) and the regional lymph node status was pN0.

Table 34. Summary of PFS and OS in studies with HR status data available

Study	Median PFS (95% CI)		Median OS (95% CI)	
	HR-negative	HR-positive	HR-negative	HR-positive
EGF104900				
Lapatinib + Trastuzumab	15.4 wks (8.4-16.9)	7.9 wks (6.3-15.7)	17.2 mos (13.9-19.2)	12.0 mos (9.4-15.4)
Lapatinib	8.2 wks (7.4, 9.3)	8.1 wks (6.1-9.9)	8.9 mos (6.7-11.8)	11.2 mos (8.0-15.4)
Hazard Ratio (95% CI)	0.73 (0.52-1.03)	0.73 (0.51-1.04)	0.62 (0.42-0.90)	0.84 (0.58-1.23)
EGF100151				
Lapatinib + Capecitabine	31.3 wks	26.7 wks	76.4 wks (66.0-87.3)	74.0 wks (58.3-95.6)
Capecitabine	17.6 wks	18.6 wks	62.6 wks (44.0-75.0)	62.1 wks (50.6-NR)
Hazard Ratio (95% CI)	0.48 (0.32-0.72)	0.61 (0.39-0.95)	0.85 (0.63-1.15)	0.86 (0.63-1.17)
EGF104535				
Lapatinib + Paclitaxel	9.4 mos (7.6-11.8)	10.7 mos (9.2-11.4)	28.1 mos (22.0-33.6)	26.2 mos (21.4-35.7)
Paclitaxel	5.4 mos (3.7-6.5)	7.3 mos (6.3-7.7)	17.4 mos (14.8-21.9)	22.9 mos (18.9-29.0)
Hazard Ratio (95% CI)	0.51 (0.38-0.68)	0.53 (0.40-0.71)	0.66 (0.47-0.93)	0.85 (0.60-1.20)

Abbreviations: CI=confidence interval; HR=hormone receptor; OS=overall survival; PFS=progression free survival;

Hormone receptor status and histology

There was a total of 88 patients with HR negative status and poor differentiation. In this subgroup the HRs dual blockade versus lapatinib monotherapy were 0.62 (95% CI 0.39; 0.97) for PFS and 0.59 (95% CI 0.37; 0.96) for OS. The ORR rates were 4 and 10% respectively, mono versus dual therapy.

Hormone receptor status and HER2 expression level

Table 35. EGF104900: HER2 IHC scores relative to tumour hormone receptor status

	HER2 FISH-positive Population with HER2 IHC Status and HR Status	
	HR-Positive (N=106)	HR-Negative (N=107)
HER2 IHC Score, N (%)		
IHC 3+	70 (66)	87 (81)
IHC 2+	24 (23)	17 (16)
IHC 1+	6 (6)	2 (2)
IHC 0	6 (6)	1 (1)
HER2 IHC Subgroup, N (%)		
IHC3+/2+	94 (89)	104 (97)
IHC1+/0	12 (11)	3 (3)

Abbreviations: FISH= fluorescence *in-situ* hybridization; HER2 = human epidermal growth factor receptor 2; HR=Hormone Receptor; IHC=Immunohistochemistry

Table 36. EGF104900: HER2 IHC scores relative to tumour differentiation status

	HER2 FISH-positive Population with HER2 IHC Status	
	Well/Moderately Differentiated N=53	Poorly/Un-differentiated N=113
HER2 IHC Score, N (%)		
IHC 3+	35 (66)	89 (79)
IHC 2+	14 (26)	16 (14)
IHC 1+	3 (6)	2 (2)
IHC 0	1 (2)	6 (5)

Abbreviations; FISH = fluorescence in-situ hybridization; HER2 = human epidermal growth factor receptor 2 ; IHC = immunohistochemistry

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for trial EGF104900

Title: A randomised, multicenter, open-Label, phase III study of lapatinib in combination with trastuzumab versus lapatinib monotherapy in subjects with metastatic breast cancer whose disease has progressed on a trastuzumab-containing regimen		
Study identifier	EGF104900	
Design	randomised, multicenter, open-label, controlled	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	<time> not applicable not applicable
Hypothesis	Superiority	
Treatment groups	Lapatinib in combination with trastuzumab (dual blockade arm) (L+T)	Lapatinib: 1000 mg (4 tablets) daily Trastuzumab: loading dose on Day 1 of 4 mg/kg IV infusion approximately 90 minutes, followed by 2 mg/kg IV infusion approximately 30 minutes weekly. N= 148
	Lapatinib monotherapy (L)	1500 mg (6 tablets) daily N=148
	Cross over period (patients cross over from lapatinib monotherapy arm to dual blockade arm)	Before cross-over: 1500 mg (6 tablets) daily After cross-over: lapatinib: 1000 mg (4 tablets) daily; trastuzumab: loading dose on Day 1 of 4 mg/kg IV infusion approximately 90 minutes, followed by 2 mg/kg IV infusion approximately 30 minutes weekly. N=77

Endpoints and definitions	Primary endpoint	PFS	Progression Free Survival: time from randomisation until the first documented sign of disease progression or death due to any cause
	Secondary endpoint	OS	Overall Survival: time from randomisation until death due to any cause. For subjects who did not die, time to death was censored at the time of last contact
	Secondary endpoint	ORR	Overall Tumour Response Rate: percentage of subjects experiencing either a confirmed CR or confirmed PR. Subjects with an unknown or missing response were treated as non-responders.
	Secondary endpoint	CBR	Clinical Benefit Response Rate: percentage of subjects with a confirmed CR or PR at any time or SD for at least 24 weeks
Database lock	PFS, ORR, CBR: cut-off date 29 June 2007 OS: cut-off date 23 January 2009		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Dual blockade arm (L+T)	Lapatinib monotherapy (L)	Cross over period[a]
	Number of subjects	148	148	77
	PFS[b], weeks (median)	12.0	8.1	6.9
	(95% CI)	(8.1, 16.0)	(7.6, 9.0)	(4.1, 8.1)
	OS[c], months (median)	14.0	9.5	10.8
	(95% CI)	(11.9, 17.2)	(7.6, 12.0)	(8.7, 15.6)
	ORR[b], %	10.3	6.9	2.7
	(95% CI)	(5.9, 16.4)	(3.4, 12.3)	(0.3, 9.5)
	CBR[e], %	24.7	12.4	8.2
	(95% CI)	(17.9, 32.5)	(7.5, 18.9)	(3.1, 17.0)

Effect estimate per comparison	PFS[b] (median)	Comparison groups	L+T versus L
		Hazard ratio	0.73
		(95% CI)	(0.57, 0.93)
		Log rank p-value	0.008
	OS[c] (median)	Comparison groups	L+T versus L
		Hazard ratio	0.74
		(95% CI)	(0.57, 0.97)
		Log rank p-value	0.026
	ORR[b]	Odds ratio	1.5
		(95% CI)	(0.6, 3.9)

		p-value	0.465
	CBR[e]	Comparison groups	L+T versus L
		Odds ratio p-value	2.2
		(95% CI)	(1.2, 4.5)
		P-value	0.01
Notes	a. For crossover patients, PFS, overall tumour response, and clinical benefit response is based on the interval between crossover and next progression while OS is based on the time interval from randomization to death. b. Data from cut-off date 29 June 2007. c. Overall survival is defined as the time from the date of randomization until death due to any cause or to date of censor. Data from cut-off date 23 January 2009. e. Investigator assessed: the percentage of subjects with confirmed complete response or partial response at any time or stable disease for at least 24 weeks. Data from cut-off date 29 June 2007.		

Table 38. Summary of PFS and OS in Studies with Hormone Receptor negative for Study EGF104900

	Median PFS (95% CI)	**Median OS (95% CI)**
Lapatinib + Trastuzumab	15.4 weeks (8.4, 16.9)	17.2 months (13.9, 19.2)
Lapatinib	8.2 weeks (7.4, 9.3)	8.9 months (6.7, 11.8)
HR (95% CI)	0.73 (0.52, 1.03)	0.62 (0.42, 0.90)

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis across trials was submitted.

Clinical studies in special populations

No studies in special population were submitted.

Supportive studies

Study LPT109096

Study LPT109096 was a phase II randomised, multicenter, open-label, trial of neoadjuvant trastuzumab and/or lapatinib plus chemotherapy (sequential FEC75 and paclitaxel) in women with ErbB2 (HER2) overexpressing invasive breast cancer.

Eligible subjects were women with invasive (T2-4, N0-2, M0 or Tx, N2 whose lymph nodes would be accessible for biopsy) human epidermal growth factor receptor-2 (HER2) overexpressing breast cancer.

The study started on 13 August 2007 and was completed on 15 October 2010.

A total of 100 subjects were randomly assigned 1:1:1 to the following treatment arms:

• Arm 1 (control): 2 weeks of trastuzumab alone (T) followed by 12 weeks of trastuzumab plus FEC75 followed by 12 weeks of trastuzumab plus paclitaxel

• Arm 2 (comparator): 2 weeks of lapatinib alone (L) followed by 12 weeks of lapatinib plus FEC75 followed by 12 weeks of lapatinib plus paclitaxel

• Arm 3 (comparator): 2 weeks of trastuzumab and lapatinib (T+L) followed by 12 weeks of trastuzumab and lapatinib plus FEC75 followed by 12 weeks of trastuzumab and lapatinib plus paclitaxel.

Criteria for efficacy assessments were pathological complete response (pCR), clinical complete response (cCR), overall response rate (ORR), and disease free survival (DFS).

Efficacy results

The ITT-E population ("evaluable": subjects who completed at least 75% chemotherapy and protocol-specified surgery, (N=26 (T), 29 (L), 23 (T+L)) was used for the primary efficacy analyses, and the ITT population was used for the secondary efficacy analyses. The primary efficacy endpoint was overall pCR (breast and lymph nodes) at the time of surgery. It is to be noted that the study was not powered for inference testing. Secondary endpoints are shown below.

Results are summarised in Table 40.

Table 39. Summary of efficacy outcomes in study LPT109096

Study LPT109096	T	L	T+L
n	33	34	33
pCR, breast + nodes (ITT-E, primary) % (CI)	54 (33.4, 73.4)	45 (26.4, 64.3)	74 (51.6, 89.8)
pCR, breast + nodes (ITT) % (CI)	55 (36.4, 71.9)	38 (22.2, 56.4)	55 (36.4, 71.9)
pCR, breast only (ITT-E) % (CI)	54	52	74
pCR, breast only (ITT), % (CI)	55	47	55
ORR, % (ITT)	61	68	61
ORR, % (E-ITT)	62	76	70
cCR, % (ITT)	42	38	36
cCR, % (E-ITT)	46	45	43

Study EGF106903 (NeoALTTO)

Study EGF106903 was a parallel group, three-arm, randomised, multi-centre, open-label phase III study comparing the efficacy of neoadjuvant lapatinib plus paclitaxel, versus trastuzumab plus paclitaxel, versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment in HER2/ErbB2 over-expressing and/or amplified primary breast cancer.

The study started on 5 January 2008 (First Subject First Visit) and was completed on 27 May 2010 (Last Subject Last Visit).

A total of 455 subjects were randomised, in accordance with the randomisation schedule, to one of the following neoadjuvant study treatments:

• Treatment Arm A — oral lapatinib (1500 mg daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg/m^2 iv) for an additional 12 weeks;

• Treatment Arm B — trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m^2 iv) for an additional 12 weeks;

• Treatment Arm C — oral lapatinib (1000 mg daily) plus trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by lapatinib (750 mg daily) plus trastuzumab (2 mg/kg iv weekly) plus weekly paclitaxel (80 mg/m^2 iv) for an additional 12 weeks.

Subjects were randomised to receive lapatinib, trastuzumab or lapatinib plus trastuzumab for a total of 6 weeks. After this biological window, subjects continued on the same targeted therapy plus weekly paclitaxel for a further 12 weeks, until definitive surgery (total neoadjuvant therapy duration of 18 weeks). Paclitaxel may have been initiated at week 4 if there is evidence of progressive disease (PD) at that time. Within 6 weeks after surgery, subjects received 3 cycles of adjuvant 5-flourouracil, epirubicin and cyclophosphamide (FEC) followed by the same targeted therapy as in the biological window of the neoadjuvant phase for a further 34 weeks (to complete 52 weeks of anti-HER2 therapy).

Criteria for evaluation

The primary endpoint was pathological complete response (pCR), defined according to NSABP guidelines as no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen.

Loco-regional pCR was a secondary endpoint, defined as having both an NSABP definition of pCR and a regional lymph node status at surgery of pN0. Some of the other secondary endpoints are shown in Table 40.

ORR was assessed using the World Health Organization (WHO) criteria. According to the protocol, bi-dimensional tumour measurements were obtained through clinical examination (breast palpation) at screening, at Weeks 2, 4, 6, 10, 13, and 16 and immediately prior to surgery; and by mammography and breast echography at screening, at Week 6 and immediately prior to surgery.

Table 40. Summary of efficacy outcomes in study EGF106903

Study EGF106903	T	L	T+L
n	149	154	152
pCR, % (CI)	29.5	24.7	51.3
Odds (SE) ratio vs. T	-	0.78 (0.21)	2.63 (0.65)
p-value vs.T	-	0.355	<0.001
Locoregional pCR	27.6	20.0	46.9
Odds (SE) ratio vs. T		0.66 (0.19)	2.40 (0.61)
p-value vs.T	0.142		<0.001
Node neg at surgery (%)	58.6	51.8	73.0
ORR at surgery (%)	70.47	74.03	80.26
Odds (SE) ratio vs. T	-	1.21 (0.32)	1.74 (0.48)
p-value vs.T	-	0.459	0.045
cCR at surgery (%)	24.16	33.12	52.63
p-value vs.T		0.0850	<0.0001

2.3.6. Discussion on clinical efficacy

Design and conduct of study EGF104900

The pivotal study was performed in a HER2-positive late stage metastatic study population with poor prognosis and limited treatment options, having already progressed on combination therapy with trastuzumab in the metastatic setting. The lapatinib dose for the combination with trastuzumab standard dose was selected based on a pre-specified level of dose-limiting toxicities in the phase I study EGF10023 which is considered justified. The inclusion and exclusion criteria, randomisation procedure and objectives of study EGF104900 are acceptable. Standard statistical methods were used for the conduct of the study and the main efficacy endpoints (PFS, OS, RR and CBR) are considered appropriate by the CHMP. PFS by investigator assessment as primary endpoint is satisfactory since independent review was also performed allowing for sensitivity analyses of the robustness of the results.

The primary efficacy analysis was defined in the protocol as the stratified log rank analysis. The study population for the primary analyses was the ITT population. Since full stratification data were missing for 5 patients, their data were automatically excluded in the primary analysis in the ITT population. In this application (however not in the original CSR) the MAH chose to also exclude these patients in the Kaplan-Meier analyses and introduced this as a new population, the "ITT population with strata". Through this measure the same number of patients is contributing to the main analyses.

Standard therapy in HER2-positive metastatic breast cancer involves HER2-blockade in combination with chemotherapy or hormonal therapy. However, the control arm in this study was an anti-HER2 monotherapy without established efficacy and with a modest activity. Therefore, it raised questions as to the interpretation of the magnitude of the dual blockade treatment benefit. At the time study EGF104900 was designed data were available supporting the use of lapatinib monotherapy in HER2-positive metastatic breast cancer from the study EGF20009. This study showed that lapatinib monotherapy had activity in HER2 metastatic breast cancer, with an investigator-evaluated ORR of 24.6% (95% CI: 15.1, 36.5). Subjects were eligible only after progression on trastuzumab containing regimens.

The decision to not include chemotherapy alone as a third arm was based on its assumed limited benefit in this population of late line and late stage disease. By adding a third arm with lapatinib in combination with chemotherapy valuable information would have been generated putting the efficacy of dual anti-HER2 treatment into perspective of other available treatment modalities.

The study results however should be interpreted in the light of current clinical practice (see below).

Efficacy results from study EGF104900

The added treatment effect of the combination treatment with trastuzumab and lapatinib compared with lapatinib as single agent was relatively small with regard to PFS. The difference in median PFS was 3.9 weeks in the primary analysis, and the HR was 0.73 (95% CI: 0.57, 0.93). The magnitude of the treatment effect was consistent in the supportive analyses by independent review and in the PP population.

The added treatment effect of the combination treatment with trastuzumab and lapatinib compared with lapatinib as single agent was considerably higher for OS (4.5 months) compared with PFS (3.9 weeks). PFS and OS results were robust with regard to sensitivity analyses. Clinical activity was shown for both treatment arms in terms of ORR with 6.9% versus 10.3% in the lapatinib monotherapy and combination arms respectively. A relevant difference in response rate between arms was only apparent in patients with two or less prior regimens in the metastatic setting, although statistically significance was not achieved in subgroups. Regarding QOL, comparison of QOL summary scores in terms of changes from baseline revealed no clinically significant differences between the treatment arms.

Further analyses were conducted in order to explain the unusual pattern observed between PFS and OS results, and particularly provide reassurance that the OS effect was attributable to the study treatment.

The types of PFS events were mainly balanced between the two arms. As expected, the majority of PFS events were due to disease progression and no relevant difference in PFS events between the two arms were observed, i.e. progression versus deaths. Neither was there any major difference in sites of disease progression observed or reasons for progressive disease. Losses to follow-up were small and balanced between the two groups and unlikely to have had an impact on PFS.

A moderate imbalance in post-study therapy was observed in the ITT population as more subjects in the dual blockade arm received treatment post-study (chemotherapy and hormone therapy) and also stayed slightly longer on therapy. On the other hand, as expected, more subjects in the lapatinib arm received anti-HER2 agents (due to the cross over design). Based on these results, the CHMP concluded that next-line therapy was of no relevant importance for the overall survival comparison.

Lapatinib had previously shown activity in subjects who progressed on trastuzumab as monotherapy (Blackwell, 2009), and in combination with capecitabine (Geyer, 2007). Furthermore, in the pivotal study investigator-evaluated best overall tumor response rate (ORR) was 6.9% in the lapatinib monotherapy arm. A clinical benefit rate (CBR) of 12.4% (CR or PR or stable disease ≥24 weeks) and a median overall survival of 9.5 months in this heavily pre-treated population was observed. Additionally, the number of fatal adverse events (which do not comprise death due to disease progression) between the arms was low and balanced (3 deaths in the dual blockade arm versus 2 deaths in the lapatinib arm). Therefore, there was no evidence of a deleterious effect of lapatinib.

There is external evidence showing that the discrepancy between OS and PFS is no unique observation. Similar discrepancies between PFS and OS have been reported in another study evaluating a different dual blockade combination (pertuzumab + trastuzumab) (Swain 2013).

Subgroup analyses

Undifferentiated or poorly differentiated histological grades (indicative of a poor prognosis) were reported in 57% of subjects in the lapatinib arm and in 45% of subjects in the dual blockade arm. A subgroup analysis was conducted in order to evaluate potential implications on the efficacy endpoints. A benefit for the dual blockade was observed in subjects with poorly/undifferentiated tumours in terms of PFS and OS, while for ORR there appeared to be a benefit in subjects with well/ moderately differentiated tumours. Data from lapatinib studies that did not include dual blockade do not suggest any association between the efficacy of lapatinib and tumour histological differentiation.

Data from exploratory analyses in the pivotal study were suggestive of an increased overall benefit for subjects with serum HER2 ECD concentrations >15 ng/mL. The mean percentage change of HER2 ECD from baseline to week 4 was highly variable. In addition, the mean changes in serum HER2 ECD from baseline and at subsequent treatment visits after week 4 were not evaluated. Based on the available data, a clear association between serum concentrations of HER2 ECD >15 ng/ml and an improved clinical outcome in HER2 positive MBC has not been established and serum HER2 ECD concentration has not been confirmed as predictive of activity of dual blockade. In relation to the gene expression analysis, because of the limitations in sample size, establishing the utility of measuring HER2 and MMP7 at the transcriptional level would require additional analyses in larger populations.

The efficacy of the dual blockade in terms of OS and ORR was increased in subjects with hormone receptor-negative tumours compared to those with hormone receptor-positive tumours, although the hazard ratios for PFS were similar (0.73). This is further supported by results from study EGF106903 (NeoALLTO) although this study was conducted in a different setting with a different endpoint (pCR). In general, data from studies with lapatinib as a sole HER2 blocking agent (in combination with chemotherapy) showed an increase in benefit in subjects with hormone receptor-negative tumours. Similar observations were made in another dual blockade combination, trastuzumab in combination with pertuzumab. Although the comparison might be limited due to the different mechanism of action between lapatinib and pertuzumab, in both the Cleopatra study, a phase III study in first line MBC (Baselga, 2012) and the neo-adjuvant Neo-Sphere study (Gianni, 2012), the combination of pertuzumab and trastuzumab showed an increase in magnitude of benefit in subjects with hormone receptor-negative tumours as compared to those with hormone receptor-positive tumours.

A benefit for dual blockade was observed in subjects with poorly differentiated/ undifferentiated tumours compared to well/moderately differentiated tumours in terms of medians for PFS and OS which was reflected in hazard ratios of 0.50 versus 0.80 for PFS and 0.70 versus 1.04 for OS respectively. For ORR, however, there appeared to be a benefit for dual blockade in subjects with well/moderately differentiated tumours. Data in support of the observed benefit in poor/ undifferentiated tumours are limited to one neo-adjuvant study, EGF106903 (pCR). There are no other external data to corroborate or refute this observation. Hence, a clear association between the efficacy of dual blockade and tumour histological differentiation has not been confirmed. It is acknowledged, however, that there is a substantial overlap between hormone receptor negative and poorly differentiated tumours. Similarly available data indicate higher expression levels of HER2 in these groups of tumours.

The CHMP considered the mechanistic grounds for the post study treatment effect and the relationship between grade of tumour differentiation, HR status and ECD and activity should be further investigated. A mechanistic understanding to the outstanding issue of whether dual blockade could modulate the effect of subsequent therapy, in particular to partially reverse resistance to chemotherapy should be further explored. Therefore a study to evaluate biomarkers of drug resistance will be conducted by the MAH as a post-authorisation measure obligation (see Annex II).

Supportive studies

The two supporting studies were performed in the neoadjuvant setting comparing lapatinib, trastuzumab, and lapatinib in combination with trastuzumab, with pathological complete response (pCR) at definitive surgery as the primary endpoint. The pCR results showed a superior outcome for the combination treatment. The lapatinib arm had numerically (but not statistically significantly) inferior pCR results compared to the trastuzumab arm in both studies. Interestingly, a different pattern was seen for ORR (radiological/clinical), where lapatinib was numerically better than trastuzumab, and similar to the combination.

Additional expert consultation

The SAG Oncology was invited to discuss the plausibility and the relevance in terms of clinical efficacy of the observations made based on the subgroups analyses provided by the MAH regarding hormone receptor status and tumour histological differentiation. The SAG agreed that the trial had met its primary efficacy objective in terms of PFS, although the observed difference between treatments was small. The analysis of the secondary endpoint OS showed a larger effect. However, the SAG views were split concerning the validity of this finding as well as about the validity of the control arm of lapatinib alone.

According to one view, the PFS results were in broad agreement with OS and the apparent discordance in terms of magnitude of the effect was not expected to have an adverse impact on the validity of OS as the surrogacy of PFS for OS has not been established. As such, findings in terms of OS were considered reliable in view of the size of the effect and the robustness of this objective endpoint. The fact that the study was designed in a time period when single arm lapatinib was accepted by many institutions as an acceptable study arm, e.g., in the adjuvant “ALLTO” study, was also acknowledged.

According to an opposing view, the apparent discordance between PFS and OS may be due to a number of reasons, including uncertainty in the adjudication of PFS (particularly in the presence of clinical progression) and uncertainty in the mechanism of action of the combination. More importantly, however, the apparent substantial effect on OS might be due to bias caused by imbalance in post-PD therapies, as many patients received one or even more lines of post-PD chemotherapy, or even a chance finding. In addition, the observed effects of the lapatinib-trastuzumab combination over a sub-

optimal comparator were not considered informative about the benefits of this combination compared to more active therapeutic options.

Concerning hormone receptor status and tumour histological differentiation, the SAG considered that the observed effect in these exploratory subgroup analyses can only be hypothesis generating, in particular in the absence of sound mechanistic basis to support these findings.

The SAG opinion was sought on whether a biomarker study would be sufficient to address the issue if treatment of patients with dual blockade could modulate the effect of subsequent therapy, in particular to partially reverse resistance to chemotherapy (in a sense chemo-sensitising), or if a clinical outcome study would be preferable. The SAG agreed about the usefulness of a clinical outcome study to confirm the role of any biomarkers and highlighted the importance of the choice of biomarkers to ensure that adequate conclusions can be drawn from such a study. In order to understand the therapeutic value of the combination of lapatinib and trastuzumab, comparison with other possible treatment options for the defined patient population should be considered.

2.3.7. Conclusions on the clinical efficacy

On the basis of the available efficacy data and considering the different views expressed by the SAG, the CHMP concluded that the reported survival benefit was of clinical relevance and could be attributed to lapatininb in combination with trastuzumab based on the clear efficacy results observed from the pivotal study, the pharmacodynamic rationale, and supportive data from clinical studies in relevant settings. The CHMP concluded that the available evidence was enough to rule out that the observed effect was largely due to the small imbalance in post-progression treatment observed. Similarly, the CHMP concluded that enough corroborative evidence was available from the pivotal clinical trial (qualitative concordance of important efficacy endpoints PFS and OS) and from supportive studies in related conditions as well as pharmacodynamic evidence, to rule out that the observed effect could be a chance finding (the latter possibility had been raised by one of the different views of the SAG).

The CHMP acknowledged (as noted by the SAG) that the results of exploratory analyses have to be interpreted with caution. Notwithstanding this limitation, results from subgroup analyses have suggested an increased benefit in patients with hormonal receptor negative tumours. More importantly, however, taking into account the design of the pivotal study and particularly the absence of endocrine-based therapy as reference regimen the use of dual blockade in subjects with hormone receptor-positive tumours was not considered adequately justified, especially in the light of the availability of combined hormonal and HER2 targeting therapy. Therefore, the CHMP concluded that the benefit of lapatinib in combination with trastuzumab has been adequately shown in patients with hormone receptor-negative metastatic disease only.

In addition, the claimed indication was amended to adequately reflect that dual HER2 blockade can be used only following prior standard of care in the metastatic setting i.e. HER2 blockade in combination with chemotherapy in line with the study population in the trial EGF104900.

The CHMP considered that the mechanistic grounds for the post study treatment effect and the relationship between grade of tumour differentiation, HR status and ECD and activity should be further investigated and the MAH was requested to evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy. The draft study protocol is expected September 2013 and the final results in June 2018.

2.3.8. Clinical safety

Introduction

The safety database for the present application consisted of 901 subjects treated in four studies evaluating patients with HER2- positive breast cancer. Of these 901 patients, a total of 386 received the combination of lapatinib and trastuzumab and of those, 370 patients received the dose of lapatinib 1000 mg which is the dose proposed for this indication. Furthermore, 334 patients received lapatinib monotherapy while 181 patients received trastuzumab monotherapy. The studies submitted for the safety assessment are the following: phase I study EGF10023, pivotal phase III study EGF104900, two supportive phase III and phase II studies (EGF106903 and LPT109096).

Each of these studies evaluated the use of lapatinib in combination with trastuzumab in women with HER2-positive breast cancer but with differences in patient population and treatments. While the pivotal study EGF104900 and the supportive study EGF10023 utilised only HER2 blocking substances in a population of heavily pre-treated metastatic breast cancer patients, the supporting studies EGF106903 and LPT109096 were conducted in the neoadjuvant setting in combination with chemotherapy in a study population consisting of treatment naive patients at study entry.

In the pivotal study, crossover to the combination trastuzumab+lapatinib (L+T) was allowed when progression occurred (defined as progression by radiological imaging and/or photography after at least 4 weeks of lapatinib monotherapy treatment). At four weeks after the initial randomisation to the lapatinib arm, 26% crossed over to the combination arm, 26% between the period four to eight weeks and 48% after eight weeks. At crossover, the lapatinib dose was reduced from 1500mg to 1000mg according to the protocol. The safety data for the 77 subjects that opted to crossover was reported separately by the MAH.

The safety population in the pivotal study included all subjects who received at least one dose of study treatment and was based on the actual treatment received if this differed from that to which the subject was randomised.

Only safety data from the pivotal study EGF104900 are presented in this report as relevant to the present application.

Patient exposure

Table 41. Study EGF104900 Exposure to study medication (Safety Population)

	Combination arm (N=149)		Monotherapy arm (N=146)
Medication	**Lapatinib 1000 mg**	**Trastuzumab**	**Lapatinib 1500 mg**
Duration of Treatment			
n	149	147[a]	146
Mean (SD), weeks	20.0 (28.03)	18.9 (27.84)	13.4 (16.16)
Median, weeks	12.3	11.3	8.1
Range, weeks	1 to 211	0 to 208	1 to 138
Daily Dose			
n	149	Not dosed daily	146
Mean (SD), mg	996.2 (67.61)	Not dosed daily	1488.8 (60.37)
Median, mg	1000.0	Not dosed daily	1500.0
Range, mg	765 to 1500[b]	Not dosed daily	1000 to 1500
Cumulative Dose			
n	149	147	146
Mean (SD), mg	136417.8 (194555.9)	49.1 (125.32)	136561.6 (169151.5)
Median, mg	78000.0	24.0	84000.0
Range, mg	4000 to 1474000	2 to 1191	13500 to 1447500

[a] Two subjects were randomised to the combination arm and received lapatinib, but did not receive trastuzumab

[b] One subject received 1500 mg lapatinib in combination with trastuzumab. During the treatment period, no AEs or SAEs were reported and the subject discontinued study treatment due to disease progression.

Table 42. Study EGF104900 Exposure to lapatinib and trastuzumab (Crossover population)

	Trastuzumab (N=77)	Lapatinib 1000 mg (N=77)
Duration of Treatment		
n	77	74
Mean (SD), weeks	13.1 (21.62)	14.3 (21.55)
Median, weeks[a]	6.7	7.4
Range, weeks	0 to 130	1 to 121
Daily Dose		
n	Not dosed daily	74
Mean (SD), mg	Not dosed daily	1001.1 (53.08)
Median, mg	Not dosed daily	1000.0
Range, mg	Not dosed daily	667 to 1275
Cumulative Dose		
n	77	74
Mean (SD), mg	27.7 (40.19)	96918.9 (149198.1)
Median, mg	16.0	49500.0
Range, mg	4 to 238	7000 to 830000

[a] Exposure assessed from the start of crossover to discontinuation of combination therapy.
Note: At crossover, the lapatinib dose was reduced to 1000 mg and trastuzumab was added to the regimen.

Adverse events

Table 43. Study EGF104900 - Adverse events by category (safety population)

	Number of subjects (%)	
	Safety Population[a]	
	L+T (n=149)	L (n=146)
Any AE	**140 (94)**	**132 (90)**
AEs related to study treatment	113 (76)	105 (72)
AEs leading to permanent discontinuation of study treatment	17 (11)	9 (6)
Any SAE		
SAEs related to study treatment	**40 (27)**	**24 (16)**
Fatal AEs	12 (8)	5 (3)
Fatal AEs related to study treatment	3 (2)	2 (1)
	1 (<1)	0

[a]The safety population included subjects based on the actual treatment received. Differences in the number of subjects from the ITT population were due to two subjects in the lapatinib monotherapy arm who did not receive the treatment to which they were allocated and one subject who was excluded from the combination arm as they did not receive any study treatment.

Table 44. Study EGF104900 - Adverse events related to study medication reported by ≥ 5 % of subjects in either treatment arm (safety population)

	Number of subjects (%)	
	Safety Population	
MedDRA Preferred Term	L+T (n=149)	L (n=146)
Any event	**113 (76)**	**105 (72)**
Diarrhoea	80 (54)	63 (43)
Rash	28 (19)	37 (25)
Nausea	28 (19)	27 (18)
Fatigue	22 (15)	18 (12)
Vomiting	15 (10)	15 (10)
Decreased appetite	9 (6)	13 (9)
Dry skin	7 (5)	2 (1)
Dermatitis acneiform	8 (5)	14 (10)
Ejection fraction decreased	8 (5)	1 (<1)
Pruritus	5 (3)	9 (6)
Anaemia	4 (3)	1 (<1)
Stomatitis	2 (1)	4 (3)

The majority of AEs were considered by the investigator to be treatment-related with an overall incidence similar in both the combination arm (76%) and the monotherapy arm (72%). However, some differences were noted. The most common AE related to treatment, was diarrhoea with a higher frequency in the combination arm compared to lapatinib monotherapy (54% and 43 % respectively). Diarrhoea is a known side effect to both lapatinib and trastuzumab (stated as very common in the individual SmPCs for both substances). On the other hand, rash that (also a known side effect to both individual substances) was more frequently reported in the lapatinib monotherapy arm compared to the combination arm (25% and 19% respectively).

Table 45. Study EGF104900 - Most common treatment-related adverse events (reported by ≥ 10% of subjects) in either treatment arm by maximum severity grade (safety population)

MedDRA Preferred Term	Number of Subjects (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Combination arm (N=149)					
Diarrhea	43 (29)	27 (18)	9 (6)	1 (<1)	80 (54)
Nausea	21 (14)	7 (5)	0	0	28 (19)
Rash	20 (13)	8 (5)	0	0	28 (19)
Fatigue	13 (9)	9 (6)	0	0	22 (15)
Vomiting	7 (5)	7 (5)	1 (<1)	0	15 (10)
Dermatitis acneiform	5 (3)	2 (1)	1 (<1)	0	8 (5)
Monotherapy arm (N=146)					
Diarrhea	37 (25)	16 (11)	10 (7)	0	63 (43)
Nausea	16 (11)	9 (6)	2 (1)	0	27 (18)
Rash	29 (20)	7 (5)	1 (<1)	0	37 (25)
Fatigue	11 (8)	3 (2)	4 (3)	0	18 (12)
Vomiting	7 (5)	7 (5)	1 (<1)	0	15 (10)
Dermatitis acneiform	7 (5)	7 (5)	0	0	14 (10)

With the exception of rash, overall the most common AEs were reported in a higher frequency and with a tendency to increasing severity, in the combination arm compared to the lapatinib monotherapy arm.

Adverse events in subjects who crossed over to the combination arm

In the pivotal study, 77 subjects (52%) in the lapatinib monotherapy arm opted to cross over to receive combination therapy upon disease progression. In this population, consistent with the safety population, the majority of subjects were <65 years (96%). Fifty four subjects (70%) reported AEs and thirty-one subjects (40%) had AEs that were considered treatment-related. Withdrawal from the study due to AEs occurred in six subjects (8%). SAEs were reported for 10 subjects (13%) and the most frequent SAE was ejection fraction decrease (3 patients, 4%).

Overall, the safety profile for the subjects who opted to crossover was fairly consistent with those randomised to the combination arm.

Adverse events of special interest

Cardiac, pulmonary (pneumonitis) and rash events are known class effect toxicities of agents that target EGFR and/or HER2 receptors. Diarrhoea and hepatobiliary events have been reported for small molecule tyrosine-kinase inhibitors (TKIs). Therefore, these adverse events were pre-defined in the pivotal study protocol as AEs of special interests.

Cardiac events

The study protocol specified that all National cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v3.0 ≥ grade 3 left ventricular systolic dysfunction, or left ventricular ejection fraction (LVEF) decreases of at least 20% relative to baseline measurements and below the institution's lower limit of normal (LLN), were to be reported as SAEs. LVEF assessments were performed at screening (baseline assessment), at week 8 then every 8 weeks while subjects receiving study treatment. Furthermore, a LVEF assessment was to be performed upon discontinuation of study treatment if the last assessment was ≥8 weeks from the date of the last dose.

Table 46. Study EGF104900 - Summary of number of subjects who experienced cardiac events that presented with decreased LVEF (safety population)

	Combination arm (N=149)	Monotherapy arm (N=146)
Subjects with Events, n (%)	11 (7)	3 (2)
Number of Occurrences, n (%)		
n	11	3
1	8 (73)	3 (100)
2	3 (27)	0
Maximum Severity, n (%)		
n	11	3
Grade 1	2 (18)	0
Grade 2	5 (45)	2 (67)
Grade 3	1 (9)	1 (33)
Grade 4	2 (18)	0
Grade 5	1 (9)	0
Number of Subjects with Interruptions, n (%)		
n	11	3
1	4 (36)	0
2 or more	0	0
Time of Onset (Days)[a]		
Median (range)	51.0 (32 to 899)	61.0 (57 to 347)
Duration Days		
Median (range)	29.0 (7 to 1790)	17.0 (15 to 31)

[a] Time to onset of the first cardiac event was calculated as the time from first dose of therapy to diagnosis of a cardiac event and its duration as the time from event diagnosis to event resolution.

Table 47. Study EGF104900 - Characteristics of cardiac events that presented with decreased LVEF (safety population)

	Combination arm (N=14)	Monotherapy arm (N=3)
Number of Events	14	3
Event Characteristics, n (%)		
n	14	3
Serious	11 (79)	3 (100)
Considered to be treatment-related[a]	11 (79)	2 (67)
Leading to withdrawal from the study	3 (21)	1 (33)
Fatal	1 (7)	0
Outcome, n (%)		
n	14	3
Recovered/resolved	8 (57)	3 (100)
Recovering/resolving	0	0
Recovered/resolved with sequelae	1 (7)	0
Not recovered/resolved	4 (29)	0
Fatal	1 (7)	0
Action Taken, n (%)		
n	14	3
Study treatment withdrawn	3 (21)	1 (33)
Dose reduced	0	0
Dose increased	0	0
Dose not changed	6 (43)	1 (33)
Dose interrupted	4 (29)	0
Not applicable	1 (7)	1 (33)

In the combination arm, 12 % (5/41) of the subjects with cardiac events had received prior (neo) adjuvant radiotherapy that included the heart in the irradiated field while 10 % (3/29) had received prior (neo) adjuvant radiotherapy not including the heart. 4 % (2/49) of the subjects that did not receive any (neo) adjuvant radiotherapy had cardiac events. In the lapatinib monotherapy arm the rates were essentially equal to the rates for those with cardiac events without prior radiotherapy. With respect to subjects with cardiac events that had had prior adjuvant radiotherapy that included the

heart in the irradiated field, rates were 12 % in the dual blockade arm versus 0 % in the lapatinib monotherapy arm.

Table 48. Study EGF104900 - Electrocardiogram (ECG) findings (safety population)

ECG Finding	Number of Subjects (%) Safety Population Combination arm (N=149)	Monotherapy arm (N=146)
Screening		
n evaluable	144	140
Normal	98 (68)	102 (73)
Abnormal, not clinically significant	45 (31)	37 (26)
Abnormal, clinically significant	1 (<1)	1 (<1)
End of study (at discontinuation of study treatment)		
n evaluable	61	21
Normal	34 (56)	19 (90)
Abnormal, not clinically significant	25 (41)	2 (10)
Abnormal, clinically significant	1 (2)	0
Missing	1 (2)	0

In the crossover population, 29 subjects were evaluable at the end of study and 20 (69%) had normal ECG findings. Nine subjects had abnormal ECG findings, all considered to be clinically non-significant by the investigator. Only two subjects were ≥ 65 years and one had a normal ECG and one had an abnormal but not clinically significant ECG.

Hepatobiliary events

Table 49. Study EGF104900 - Summary of number of subjects who experienced hepatobiliary events (safety population)

	Dual Blockade Arm N=149	Lapatinib Arm N=146
Subjects with Events, n (%)	16 (11)	13 (9)
Number of Occurrences, n (%)		
n	16	13
1	5 (31)	8 (62)
2	5 (31)	3 (23)
3 or more	6 (38)	2 (15)
Maximum Severity, n (%)		
n	16	13
Grade 1	2 (13)	2 (15)
Grade 2	8 (50)	4 (31)
Grade 3	6 (38)	4 (31)
Grade 4	0	1 (8)
Grade 5	0	1 (8)[a]
Unknown	0	1 (8)
Number of Subjects with Interruptions, n (%)		
n	16	13
1	2 (13)	2 (15)
2	0	0
3 or more	0	1 (8)
Time of Onset Days[b]		
Median (range)	29.0 (1-545)	28.0 (1-203)
Duration Days		
Median (range)	46.0 (20-553)	40 (2-1580)

[a] One subject died due to hepatic and renal failure and considered unrelated to study treatment by the investigator.
[b] Time to onset of the first hepatobiliary event was calculated as the time from first dose of therapy to diagnosis of a hepatobiliary event and its duration as the time from event diagnosis to event resolution.
Note: Subjects may be included in more than one category for event characteristics, outcome and action taken.

Table 50. Study EGF104900 - Summary characteristics of hepatobiliary events (safety population)

	Dual Blockade Arm N=149	Lapatinib Arm N=146
Number of Events	47	24
Event Characteristics, n (%)		
n	47	24
Serious	1 (2)	4 (17)
Considered to be treatment related [a]	9 (19)	7 (29)
Leading to withdrawal from the study	6 (13)	3 (13)
Fatal	0	1 (4)
Outcome, n (%)		
n	47	24
Recovered/resolved	29 (62)	7 (29)
Recovering/resolving	6 (13)	0
Recovered/resolved with sequelae	2 (4)	3 (13)
Not recovered/resolved	10 (21)	13 (54)
Fatal	0	1 (1) [b]
Action Taken, n (%)		
n	47	24
Investigational product withdrawn	6 (13)	3 (13)
Dose reduced	0	0
Dose increased	0	0
Dose not changed	36 (77)	12 (50)
Dose interrupted	2 (4)	7 (29)
Not applicable	3 (6)	2 (8)

[a] If CRF data were missing, it was assumed that AEs were related to the study treatment.
[b] One subject died due to hepatic and renal failure
Note: Subjects may be included in more than one category for event characteristics, outcome and action taken.

In the crossover population, eight hepatobiliary events were reported in two subjects (3%). One subject had events reported as clinically significant hepatic laboratory abnormalities of grade 3 and 4, and all resolved including a grade 4 SAE of jaundice cholestatic. All other events were hepatic laboratory abnormalities. Six events led to dose interruptions. The other subject had two events which resolved with sequelae.

None of the events led to withdrawal from study.

Hepatobiliary laboratory abnormalities

The criteria for reporting elevations in hepatic enzymes as an SAE was defined as: ALT ≥3 x ULN and total bilirubin ≥2.0 x ULN (>35% direct; bilirubin fractionation was required where testing was available).

A similar proportion of subjects in both treatment arms had at least one pre-defined hepatobiliary laboratory abnormality (Table 51).

Table 51. Study EGF104900 - Summary of subjects with hepatobiliary laboratory abnormalities (Safety Population)

Laboratory criteria	Dual Blockade Arm N=149	Lapatinib Arm N=146
Any Event	37 (25)	34 (23)
Possible Hy's Law:		
≥3x ULN AST & or ALT & ≥2x ULN total BIL & ALP <2x ULN	0	0
≥3x ULN AST & or ALT & ≥2x ULN total BIL & ALP missing	0	0
ALT, AST & Total Bilirubin Elevations		
≥3x ULN AST & or ALT & ≥1.5x ULN total BIL	5 (3)	5 (3)
≥3x ULN AST & or ALT & ≥2x ULN total BIL	4 (3)	4 (3)
ALT & AST Elevations		
≥3x ULN	4 (3)	5 (3)
≥5x ULN	2 (1)	1 (<1)
≥10x ULN	1 (<1)	0
≥20x ULN	1 (<1)	0
ALT Elevations		
≥3x ULN	6 (4)	6 (4)
≥5x ULN	2 (1)	2 (1)
≥10x ULN	1 (<1)	1 (<1)
≥20x ULN	1 (<1)	0
AST Elevations		
≥3x ULN	13 (9)	13 (9)
≥5x ULN	6 (4)	7 (5)
≥10x ULN	1 (<1)	1 (<1)
≥20x ULN	1 (<1)	0
Total Bilirubin Elevations		
>1.5x ULN	9 (6)	7 (5)
>2x ULN	6 (4)	6 (4)
ALP Elevation		
>1.5x ULN	33 (22)	32 (22)

The frequency of reported hepatobiliary abnormalities was similar between the treatment arms and none met the criteria for Hy's Law.

Interstitial lung disease and pneumonitis

Pulmonary SAEs, including interstitial lung disease and pneumonitis, are associated with both lapatinib and trastuzumab. In one subject (1%), one grade 2 event of pneumonitis was reported in the crossover population. The event subsequently resolved without a dose reduction or discontinuation of study treatment and was not considered serious or related to treatment.

Rash

Table 52. Study EGF104900 - Summary of number of subjects who experienced rash events (Safety Population)

	Safety Population	
	Combination arm (N=149)	Monotherapy arm (N=146)
Subjects with Events, n (%)	35 (23)	43 (29)
Number of Occurrences, n (%)		
n	35	43
1	28 (80)	34 (79)
2	4 (11)	8 (19)
3 or more	3 (9)	1 (2)
Maximum Severity, n (%)		
n	35	43
Grade 1	27 (77)	34 (79)
Grade 2	8 (23)	8 (19)
Grade 3	0	1 (2)
Grade 4	0	0
Grade 5	0	0
Number of Subjects with Interruptions, n (%)		
n	35	43
1	0	4 (9)
2	0	0
3 or more	0	0
Time of Onset Days [a]		
Median (range)	24.0 (1 to 257)	19.0 (2 to 189)
Duration Days		
Median (range)	49.0 (1 to 1655)	29.0 (3 to 1600)

a. Time to onset of the first rash event was calculated as the time from first dose of therapy to diagnosis of a rash event and its duration as the time from event diagnosis to event resolution.
Note: Preferred terms of acne, dermatitis, eczema, erythema, folliculitis, rash, rash papular, and rash pustular are included.

Table 53. Study EGF104900 - Summary characteristics of rash events (Safety Population)

	Safety Population	
	Combination arm (N=48)	Monotherapy arm (N=55)
Number of Events	48	55
Event Characteristics, n (%)		
n	48	55
Serious	0	0
Considered to be treatment-related[a]	36 (75)	45 (82)
Leading to withdrawal from the study	0	0
Fatal	0	0
Outcome, n (%)		
n	48	55
Recovered/resolved	38 (79)	35 (64)
Recovering/resolving	3 (6)	3 (5)
Recovered/resolved with sequelae	2 (4)	1 (2)
Not recovered/resolved	5 (10)	16 (29)
Fatal	0	0
Action Taken, n (%)		
n	48	55
Investigational product withdrawn	0	0
Dose reduced	0	0
Dose increased	0	0
Dose not changed	48 (100)	51 (93)
Dose interrupted	0	4 (7)
Not applicable	0	0

[a] If CRF data were missing, it was assumed that AEs were related to the study treatment.
Note: Subjects may be included in more than one category for event characteristics, outcome, and action taken.
Note: Preferred terms of acne, dermatitis, eczema, erythema, folliculitis, rash, rash papular and rash pustular are included.

In the crossover population, nine events of rash were reported in eight subjects (10%). All events were grade 1 or grade 2, and none were considered serious. One event led to one dose interruption but no dose reductions.

Diarrhoea

Table 54. Study EGF104900 - Summary of number of subjects who experienced diarrhoea events (Safety Population)

	Safety Population	
	Combination arm (N=149)	Monotherapy arm (N=146)
Subjects with Events, n (%)	92 (62)	70 (48)
Number of Occurrences, n (%)		
n	92	70
1	60 (65)	52 (74)
2	14 (15)	12 (17)
3 or more	18 (20)	6 (9)
Maximum Severity, n (%)		
n	92	70
Grade 1	51 (55)	43 (61)
Grade 2	29 (32)	17 (24)
Grade 3	11 (12)	10 (14)
Grade 4	1 (1)	0
Grade 5	0	0
Number of Subjects with Interruptions, n (%)		
n	92	70
1	10 (11)	12 (17)
2	4 (4)	0
3 or more	0	1 (1)
Time of Onset Days[a]		
Median (range)	7.0 (1 to 779)	7.0 (1 to 126)
Duration Days		
Median (range)	19.0 (1 to 1739)	25.5 (1 to 1763)

[a] Time to onset of the first diarrhoea event was calculated as the time from first dose of randomized treatment to diagnosis of a diarrhoea event and its duration as the time from event diagnosis to event resolution.
Note: Preferred terms of diarrhoea, loose stools, and frequent bowel movements have been included.

Table 55. Study EGF104900 - Characteristics of diarrhoea adverse events

	Safety Population	
	Combination arm (N=185)	Monotherapy arm (N=98)
Number of Events	185	98
Event Characteristics, n (%)		
n	185	98
Serious	2 (1)	3 (3)
Considered to be treatment-related[a]	159 (86)	86 (88)
Leading to withdrawal from the study	0	2 (2)
Fatal	0	0
Outcome, n (%)		
n	185	70
Recovered/resolved	156 (84)	72 (73)
Recovering/resolving	4 (2)	7 (7)
Recovered/resolved with sequelae	6 (3)	6 (6)
Not recovered/resolved	19 (10)	13 (13)
Fatal	0	0
Action Taken, n (%)		
n	185	98
Investigational product withdrawn	0	2 (2)
Dose reduced	4 (2)	2 (2)
Dose increased	0	0
Dose not changed	160 (86)	79 (81)
Dose interrupted	18 (10)	15 (15)
Not applicable	3 (2)	0

[a] If CRF data were missing, it was assumed that AEs were treatment-related.
Note: Subjects may be included in more than one category for event characteristics, outcome, and action taken.
Note: Preferred terms of diarrhoea, loose stools, and frequent bowel movements have been included.

Serious adverse events and deaths

Serious adverse events

Table 56. Study EGF104900 - Serious adverse event, regardless of relationship, experienced by more than one subject (safety population)

	Number of Subjects (%)	
	Safety Population	
MedDRA Preferred Term	Combination arm (N=149)	Monotherapy arm (N=146)
Any SAE	40 (27)	24 (16)
Ejection fraction decreased	7 (5)	1 (<1)
Dehydration	4 (3)	0
Vomiting	3 (2)	2 (1)
Diarrhea	2 (1)	3 (2)
Nausea	2 (1)	2 (1)
Convulsion	2 (1)	0
Febrile neutropenia	2 (1)	0
Headache	2 (1)	0
Pulmonary embolism	2 (1)	0
Left ventricular dysfunction	1 (<1)	2 (1)
Dyspnea	1 (<1)	1 (<1)
Pleural effusion	1 (<1)	1 (<1)
Pneumonia	1 (<1)	1 (<1)
Lymphoedema	1 (<1)	1 (<1)
Jaundice	1 (<1)	1 (<1)

Table 57. Study EGF104900 - Treatment-related serious adverse events

MedDRA Preferred Term	Number of Subjects (%) Safety Population Combination arm (N=149)	Number of Subjects (%) Safety Population Monotherapy arm (N=146)
Any treatment-related SAE	12 (8)	5 (3)
Ejection fraction decreased	7 (5)	1 (<1)
Diarrhea	1 (<1)	3 (2)
Febrile neutropenia	1 (<1)	0
Nausea	1 (<1)	0
Left ventricular dysfunction	1 (<1)	1 (<1)
Cardiac failure	1 (<1)	0
Vomiting	1 (<1)	0

The only treatment-related SAEs that occurred in more than one subject, were cardiac events (including decreased ejection fraction, left ventricular dysfunction and cardiac failure) and diarrhoea.

In the crossover population, SAEs were reported for 10 subjects (13%). Ejection fraction decrease was the most frequent SAE (in 3 subjects, 4%). No other SAE was reported by more than one subject. Four subjects had SAEs that were considered treatment-related, including two subjects with ejection fraction decreases, and one subject with left ventricular dysfunction and one subject with thrombocytopenia.

Deaths

Table 58. Study EGF104900 - Summary of deaths (safety population and crossover population)

	Number of Subjects (%)		
	Safety Population[a]		Crossover population
	Combination arm (n=149)	Monotherapy arm (n=146)	(n=77)
Subject Status			
Dead	123 (83)	120 (82)	64 (83)
Death not reported	26 (17)	26 (18)	13 (17)
Primary Cause of Death			
Disease under study	117 (79)	118 (81)	63 (82)
Haematological toxicity	0	0	0
Non-haematological toxicity	1 (<1)	0	0
Other	5 (3)[b]	2 (1)[c]	1 (1)
Unknown	0	0	0
Time to Death from Last Dose			
≤30 days	14 (9)	16 (11)	8 (10)
>30 days	109 (73)	104 (71)	56 (73)
Unknown	0	0	0

[a] The number of deaths is based on the Safety Population in which subjects are analysed based on the actual treatment received. Note: One subject randomised to the combination arm did not receive any study treatment. In addition, 2 subjects who were randomised to receive monotherapy treatment inadvertently received combination therapy.
[b] Three deaths were due to fatal SAEs, 2 deaths were due to disease progression.
[c] One death was caused by disease progression, while the other death was ascribed to unknown causes

Table 59. Study EGF104900 - Fatal SAEs regardless of relationship (safety population)

	Number of subjects (%)	
	Safety Population	
MedDRA Preferred Term	**L+T (n=149)**	**L (n=146)**
Any fatal SAE	**3 (2)**	**2 (1)**
Cardiac failure	1 (<1)[a]	0
Pulmonary embolism	1 (<1)[a]	0
Respiratory failure	1 (<1)	0
Sepsis	1 (<1)	0
Hepatic failure	0	1 (<1)[b]
Renal failure	0	1 (<1)[b]
Internal injury	0	1 (<1)

[a] Both these SAEs occurred in the same subject
[b] Both these SAEs occurred in the same subject

Laboratory findings

Haematology

Overall, the majority of haematology events were of severity grade 1-2 and consistent with this study population of heavily pre-treated patients with advanced breast cancer. The most commonly reported grade 3 haematology parameter was lymphocyte count with 28 subjects in the combination arm and 13 subjects in the lapatinib monotherapy arm. In the combination arm, one subject experienced a grade 3 haemoglobin decrease while none was observed in the lapatinib arm. Concerning neutrophil count events, twelve patients exhibited grade 4 in the combination arm as compared to three patients in the lapatinib arm. Two subjects had SAEs of grade 3 febrile neutropenia of which one event was considered treatment-related (occurred following discontinuation of combination therapy, when the subject was receiving post-study treatment with nab-paclitaxel). The second event occurred within 30 days of discontinuing combination therapy and was not considered treatment-related.

Clinical chemistry

The majority of clinical chemistry events were of grade 1-2 in both treatment arms. The most commonly reported grade 3 clinical chemistry parameters were elevated alkaline phosphatase (ALP) (5% of subjects in both the combination and monotherapy arm) and elevated aspartate aminotransferase (AST) (in 3% of subjects in the combination arm, and 5% of subjects in the monotherapy arm).

Safety in special populations

Age

The vast majority of subjects were less than 65 years of age: 259 (88%) were < 65 years and 37 (12%) ≥ 65 years. Nine patients (3%) were ≥ 75 years.

Table 60. Study EGF104900 - Summary of effect of age on adverse events

Study and Treatment Regimen	AEs	AEs Leading to Discontinuation of IP	SAEs	Fatal SAEs
EGF104900				
Dual blockade, n (%)				
<65 (N=126)	118 (94)	14 (11)	33 (26)	3 (2)
≥65 (N=23)	22 (96)	3 (13)	7 (30)	0
≥75 (N=6)	6 (100)	1 (17)	2 (33)	0
Lapatinib, n (%)				
< 65 (N=132)	118 (89)	5 (4)	20 (15)	0
≥65 (N=14)	14 (100)	4 (29)	4 (29)	2 (14)
≥75 (N=3)	3 (100)	2 (67)	0	0

Safety related to drug-drug interactions and other interactions

Study EGF10023 was a phase I open-label study conducted to determine the safety, tolerability, optimally tolerated regimen (OTR), and pharmacokinetics of lapatinib and trastuzumab in combination. Fifty-four subjects with breast cancer whose tumours over-expressed HER2 were enrolled into three cohorts. The most common drug related AEs reported were diarrhoea (81%), rash (54%), fatigue (52%), and nausea (50%). No drug-related deaths were reported. No clinically significant changes were observed for any laboratory value or vital sign.

Discontinuation due to adverse events

Table 61. Study EGF104900 - Summary of adverse events leading to discontinuation of study treatment reported for ≥ 1% of subjects in either arm regardless of relationship to study medication

	Number of subjects (%)	
	Safety population	
MedDRA Preferred Term	L+T (n=149)	L (n=146)
Any AE leading to discontinuation	17 (11)	9 (6)
Blood bilirubin increase	2 (1)	0
Headache	2 (1)	0
Thrombocytopenia	2 (1)	0
Fatigue	1(<1)	2 (1)
Diarrhoea	0	2 (1)

In the pivotal study, a total of 17 subjects (11%) in the combination arm and 9 subjects (6%) in the lapatinib arm discontinued study treatment due to AEs. Discontinuations due to diarrhoea occurred only in the lapatinib arm.

In the crossover population, six subjects (8%) experienced AEs that led to treatment discontinuation. These were hypoxia, respiratory failure, thrombocytopenia, left ventricular dysfunction, asthenia, ejection fraction decreased, and back pain and each were experienced by one subject, with the exception of hypoxia and back pain that were experienced by the same subject.

Adverse events leading to dose delays for lapatinib

Table 62. Study EGF104900 - Summary of dose delays for Lapatinib (Safety Population)

	Dual Blockade Arm N=149	Lapatinib Arm N=146
Subjects with any lapatinib dose delays, n (%)	**34 (23)**	**35 (24)**
Total number of dose delays	51	47
Number of dose delays, n (%)		
0	115 (77)	111 (76)
1	25 (17)	26 (18)
2	4 (3)	6 (4)
3 or more	5 (3)	3 (2)
Not evaluable	0	0
Duration of delays (days)		
n	51	47
Median (range)	6 (1-38)	4 (1-30)
1-5 days, n (%)	23 (45)	30 (64)
6-7 days, n (%)	10 (20)	9 (19)
>7 days, n (%)	18 (35)	8 (17)
Reasons for delays[a]		
Hematologic toxicity, n (%)	9 (18)[b]	1 (2)
Non-hematologic toxicity, n (%)	23 (45)	21 (45)
Other, n (%)	19 (37)[c]	25 (35)[d]

No difference between treatment arms could be seen in regards to subjects that required dose delays. Regarding the causes for the delays, the majority were due to non-hematologic toxicity. The incidence of non-hematologic toxicity was similar between arms.

A similar dose delay and reduction profile was observed for the crossover population. Sixteen subjects (21%) had a lapatinib dose delay, and 14 subjects (18%) had a trastuzumab dose delay.

Adverse events leading to dose delays for trastuzumab

Dose delays caused by trastuzumab occurred in 40 subjects (27%) and with a total number of dose delays of 77. Median duration was 8 (range 4-22) days. The majority (25 (17%)) had only one delay. The main causes were neither hematologic (1(1%)) nor non-haematological toxicity (14 (18%)) but were referred to as “others” and amounted to a total number of dose delays of 62 (81%). “Others” encompassed a total of 39 subjects experiencing 70 instances of trastuzumab being delayed: one for haematologic toxicity, 14 for non-haematological toxicity and 55 for “other” reasons.

Thirty-seven out of 55 instances of trastuzumab administration delay were due to administrative or logistical reasons seemingly unrelated to toxicity. From the remaining instances, of delay for “other” causes, no defined pattern of adverse events could be disclosed.

Adverse events leading to lapatinib dose reductions

Out of the safety population of 149 subjects in the combination arm and 146 in the lapatinib arm, nine and five subjects respectively, required a dose reduction. The total number of dose reductions was nine in the combination arm and seven in the lapatinib monotherapy arm. The main reason for dose reduction was non-hematologic toxicity, similar in both arms. No subjects had a trastuzumab dose reduction as specified in the protocol.

2.3.9. Discussion on clinical safety

Overall, common adverse events were reported with a similar frequency between the two treatment arms with the most common adverse events being, diarrhoea, nausea, rash, fatigue and vomiting. The majority of the AEs were of severity grade 1-2, considered manageable and resolved.

Although the common AEs were reported in a similar frequency between the treatment arms, there was an increase in individual SAEs with in general a higher frequency in the combination arm compared to the lapatinib arm. The exception was rash that was reported in the lapatinib monotherapy arm to a slightly higher extent.

Due to the established toxicity profile of the two active substances, AEs of special interest were specified in the protocol and encompassed cardiac, pulmonary, hepatobiliary, rash and diarrhoea events.

In the pivotal study, a higher rate of cardiac events was observed in the combination arm, with increased severity, earlier onset and longer duration of event which also were reflected in the action taken in regards to study treatment. One fatal SAE occurred in the combination arm that was considered treatment-related. However, the majority of the cardiac events was of grade 1-2 (asymptomatic) and did subsequently resolve.

The population consisted of heavily pre-treated patients that had received numerous previous regimens prior to study entry. Since few prior radiation treatment details were collected in EGF104900 it was not possible to evaluate whether prior radiotherapy may have increased the incidence of cardiac toxicity observed in the analysis. Nevertheless, there were a limited number of subjects in the analyses and overall few cardiac events reported in EGF104900 (n=14, any grade) which was considered acceptable. In addition, cardiac events are adequately addressed in the Risk Management Plan. The current product information also reflects that the incidence of cardiac adverse events was increased with the combination treatment of lapatinib and trastuzumab compared with lapatinib monotherapy. Cardiac events (including asymptomatic and symptomatic Left Ventricular Ejection Fraction and Congestive Heart Failure) should continue to be monitored through routine pharmacovigilance activities as recommended in the last renewal (EMEA/H/C/000795/R/0028).

Regarding the observed differences between normal and abnormal ECG findings from screening until end of study between the two treatment arms, a relatively small proportion of subjects in both treatment arms had post-baseline ECGs thus hampering the possibility to identify any trends towards worsening ECG findings during the course of the study treatment. Further data were requested with regard to the potential risk of QT prolongation. Pre-clinical, clinical, and post-marketing data presented by the MAH do not suggest any synergistic effect on QTc when lapatinib and trastuzumab are combined in the clinical setting. With respect to trastuzumab, there is currently limited evidence of any clinically significant QT effect. The lack of information on the potential for lapatinib to prolong the QT interval is already addressed in the current product information (section 4.4 and 4.8 of the SmPC). The MAH will continue to monitor for reports of torsades de pointes and QT prolongation through routine pharmacovigilance activities.

One grade 2 event of pneumonitis was reported for one subject (1%) who crossed over to the combination treatment. The event subsequently resolved without a dose reduction or discontinuation of study treatment and was not considered serious or related to treatment.

Regarding hepatobiliary events, the addition of trastuzumab to lapatinib did not increase the risk and median time of onset to any large extent.

Rash events were commonly reported but more importantly, did not increase with the addition of trastuzumab to lapatinib treatment. However, while the median time to onset was similar, the median duration was longer in the combination arm. Based on the safety information available, no changes to the product information of Tyverb or additional risk management measures are warranted.

Diarrhoea was the most common reported AE (62% in the combination arm versus 48% in the lapatinib arm) though the majority was of grade 1-2. The addition of trastuzumab to lapatinib did lead to a higher frequency of AEs reported but no apparent increase in severity or duration. This is adequately reflected in section 4.8 of the SmPC. The median time to onset was also similar between both treatment arms.

As expected in this late-stage breast cancer study population, the cause of death for the majority of subjects was death by disease progression. The rates were low and similar over both treatment arms and crossover population (overall approximately 80%).

In general, the majority of the number of clinical chemistry events reported, occurred during the subsequent weeks after start of study treatment and then decreased over time, which may reflect side effects not yet resolved from the previous treatments.

Overall, AEs that led to discontinuation of study treatment were reported in a higher rate in the combination arm compared to the lapatinib arm (11% and 6%, respectively). However, none were reported by more than two subjects and no specific adverse event was reported as the cause for a discontinuation.

The study population consisted in a vast majority of patients aged under 65 years old and only approximately 10% were aged 65 years old or older. The lack of data in this special population is reflected in the section 4.2 of the SmPC and addressed in the RMP.

2.3.10. Conclusions on clinical safety

Overall, the most common adverse events observed were diarrhoea, nausea, rash, fatigue and vomiting and the increases in toxicity observed when adding lapatinib to trastuzumab were in general manageable.

The higher incidence of cardiac events, including LVEF decreases, when lapatinib was administered in combination with trastuzumab in the metastatic setting (7%) versus the lapatinib alone arm (2%) in the pivotal trial is adequately reflected in section 4.4 of the current product information. These events were comparable in nature and severity to those reported from the lapatinib clinical programme.

In conclusion, the observed toxicity profile observed in the pivotal study EGF104900 is consistent with the known toxicity profile of both lapatinib and trastuzumab and no evidence of a new safety signal was detected.

2.3.11. PSUR cycle

The PSUR cycle remains unchanged.

The Annex II to the CHMP opinion related to the PSUR refers to the EURD list which remains unchanged.

2.4. Risk management plan

The MAH submitted an updated Risk Management Plan (RMP) (version 19) in the new format within this variation procedure which includes a risk minimisation plan.

Table 63: Summary of the Safety Concerns

Summary of safety concerns	
Main identified risks	Hepatobiliary events Decreased LVEF Pneumonitis/ILD Diarrhoea Rash Interactions with Other Drugs
Main potential risks	QTc prolongation Food effect
Additional information to be provided	Children The Elderly Pregnant or lactating females Patients with hepatic disease Patients with renal disease Patients with low cardiac ejection fraction Patients of different racial and / or ethnic origin

Pharmacovigilance plan

Table 64: Measures in the Pharmacovigilance development plan

Study/activity including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Date for submission of (interim and) final results**
09DMR017 Lapatinib Metabolite Identification in Dog Plasma, Bile and Liver	To identify lapatinib metabolites in dog plasma, bile and liver.	Mechanism of hepatotoxicity	Ongoing	2Q2013
110858 (GERICO): Phase II Study Evaluating the Activity of the Combination Lapatinib plus Capecitabine in Elderly Patients Aged 70 and Older with Locally Advanced or Metastatic Breast Cancer (MBC) Over-expressing HER2+	To assess clinical benefit (defined at 4 months as complete response, partial response or stable disease), safety and preserved geriatric independence.	Use in the Elderly	Terminated	2014
Development of an animal model to study tyrosine kinase inhibitor-induced mucosal injury and diarrhoea (NCS/Keefe).	Investigation of mechanisms of TKI monotherapy-induced diarrhoea in the rat, and dose-finding for long course chemotherapy-induced diarrhoea.	Mechanism of diarrhoea	Ongoing	Estimated 2Q2012
EGF114271: A study to evaluate the effect of lapatinib on QT interval in patients with cancer.	This study is designed to estimate the effect of supra-therapeutic doses of lapatinib on QTcF interval as compared to placebo. No formal hypothesis will be tested.	Potential for QTc prolongation	Ongoing	4Q2014
EGF115152 (PGx397): Whole genome sequencing of lapatinib concurrent ALT/TBL elevation and extreme ALT elevation cases	This interim objective is to provide DRB1*07:01, DQA1*02:01 and UGT1A1*28 genotype results in selected hepatic SAE cases who presented in lapatinib clinical trials.	Risk factors for hepatotoxicity	Ongoing	2Q2013
LAP112539: A Phase II Study of Lapatinib and Bevacizumab in Children with Recurrent or Refractory Ependymoma	To estimate the sustained objective response rates (CR plus PR) to lapatinib 700 mg/m2/dose bid, bevacizumab 10 mg/kg iv q 2 weeks to children with recurrent or refractory ependymoma.	Use in children	Ongoing	Estimated 2Q2012
LAP113130 (LANTERN): A randomised phase II screening trial with	To investigate the effect of lapatinib plus capecitabine compared with trastuzumab	Concomitant use of corticosteroids	Ongoing	4Q2013

Study / activity including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Date for submission of (interim and) final results
functional imaging and patient reported toxicity sub-studies comparing LApatiNib plus capecitabine versus continued Trastuzumab plus capecitabine after local therapy in patients with ERb B2 positive metastatic breast cancer developing braiN metastasis/es.	plus capecitabine on time to progression of CNS metastases as measured by Response Evaluation Criteria In Solid Tumors (RECIST). Secondary objectives include: Total days of steroid use for palliation of CNS symptoms.	with lapatinib		
LAP114443: An open-label Phase II study of lapatinib plus trastuzumab combination in subjects of age ≥60 years with HER2-positive MBC.	To estimate the rate of grade 3 or higher toxicities in adults aged 60 or older receiving the combination of trastuzumab and lapatinib for metastatic breast cancer.	Use in the elderly	Ongoing	December 2013
EGF115925: Safety and Efficacy of the Combination of Lapatinib, Trastuzumab and Docetaxel Followed by Maintenance Lapatinib and Trastuzumab as First Line Treatment in Her2/neu Positive Metastatic Breast Cancer.	The primary objective of the study is to evaluate the safety of the combination of lapatinib, trastuzumab and docetaxel followed by maintenance lapatinib and trastuzumab as first line treatment in Her2/neu positive metastatic breast cancer. The safety criteria used is the incidence of grade 3 and 4 diarrhoea. Therefore the study has been designated as a TSS by GSK.	Diarrhoea	Planned start 1Q2013	16-Dec-2016

Risk minimisation measures

Table 65: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatobiliary Events	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of the hepatobiliary events reported, prompting evaluation and review by the SRT. - IDMCs are instructed to review hepatobiliary events for the studies they monitor. - Warning and Adverse Reaction in the SmPC. - PL includes comparable wording.	None.

Decreased LVEF	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of the hepatobiliary events reported, prompting evaluation and review by the SRT. - IDMCs are instructed to review cardiac events for the studies they monitor. - Regular cardiac monitoring by Echocardiogram/MUGA during clinical trials, and at study completion or withdrawal. - Warning and Adverse Reaction in the SmPC. - PL includes comparable wording.	None.
Pneumonitis/ILD	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of pulmonary events reported, prompting evaluation and review by the SRT. - IDMCs are instructed to review pneumonitis/ILD for the studies they monitor. - Review of pulmonary toxicity included in the remit of lapatinib IDMCs. - Warning and Adverse Reaction in the SmPC. - PL includes comparable wording.	None.
Diarrhoea	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of lapatinib associated diarrhoea, prompting evaluation and review by the SRT. - Warning and Adverse Reaction in the SmPC. - PL includes comparable wording.	None.
Rash	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of lapatinib associated rash, prompting evaluation and review by the SRT. - Adverse reaction in the SmPC. - PL includes comparable wording.	None.
Interactions with other Drugs	- Routine pharmacovigilance will be used to identify any changes in the	None

	signal for interactions with other drugs, prompting evaluation and review by the SRT. - Warning and Interactions with other medicinal products included in the SmPC. - PL includes comparable wording.	
QTc Prolongation	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of the QT related events reported, prompting evaluation and review by the SRT. - Warning included in the SmPC.	None
Food Effects	- Routine pharmacovigilance will be used to identify any signal for food related effects, prompting evaluation and review by the SRT. - Included as an Interaction in the SmPC PL includes comparable wording	None
Children	- Routine pharmacovigilance will be used to identify any paediatric events reported. - Included in posology section of the SmPC.	None
Elderly	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of adverse events reported from the elderly. - Included in posology section of the SmPC.	None
Pregnant or Lactating Females	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of pregnancy reports, prompting evaluation and review by the SRT. - Pregnancy Section in the SmPC. - PL includes comparable wording.	None
Patients with Hepatic Disease	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of events reported from patients with hepatic disease, prompting evaluation and review by the SRT. - Included in posology section of the SmPC. - PL includes comparable wording.	None

Patients with Renal Disease	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of events reported from patients with renal disease, prompting evaluation and review by the SRT. - Included in posology section of the SmPC.	None
Patients with low cardiac ejection fraction	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of events reported from patients with low LVEF at baseline, prompting evaluation and review by the SRT. - Included as a warning in the SmPC. - PL includes comparable wording.	None
Patients of different racial and / or ethnic origin	- Routine pharmacovigilance will be used to identify any changes in the reporting rate, or the nature of events reported from patients of different racial and/or ethnic origin, prompting evaluation and review by the SRT.	None

No new pharmacovigilance activities in addition to those already being performed are considered needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

The following study has been included in the risk management plan under the summary of post authorisation efficacy development plan.

Description of study	Objective	Milestones	Due dates
EGF117165: A two-arm study to evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy. Scientific advice will be sought in September 2013.	The primary objective will be to evaluate changes in biomarkers associated with drug resistance during treatment.	Draft protocol will be available in September 2013	Protocol Approved: March 2014 First Subject First Visit: August 2014 Study Report: June 2018 End of Study Report: June 2018

The RMP submitted was considered adequate by the CHMP.

2.5. Update of the Product information

The CHMP agreed to the following indication to be added in section 4.1 of the SmPC:

"Tyverb is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

• in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy (see Section 5.1)."

As a consequence of this new indication, sections 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet (PL) has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template and make minor corrections which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to add contact details for the representative of Croatia.

The originally approved package leaflet for Tyverb in combination with capecitabine has undergone full user testing in line with the applicable regulations. The proposed format and content of the package leaflet for the applied indication in combination with trastuzumab are effectively identical to that of the authorised package leaflet for the currently authorised combinations. As such, the proposed package leaflet remains consistent with previous user testing recommendations and no full user consultation with target patient groups on the package leaflet has been performed. The justification submitted by the applicant was acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pivotal study EGF104900 investigated the effect of dual HER2 blockade with trastuzumab and lapatinib versus lapatinib monotherapy in metastatic breast cancer progressing on a trastuzumab-containing regimen.

The treatment effect observed in the primary endpoint, PFS by investigator assessment, was limited to a median difference of about 4 weeks (HR 0.73 (95% CI: 0.57, 0.93). The key secondary endpoint, overall survival, showed an apparent treatment effect that was considerably more substantial, with a difference in medians of 4.5 months (HR 0.74 (0.57, 0.97)).

In subgroup analysis by hormone receptor status, an increased benefit of lapatinib and trastuzumab was observed in hormone-receptor negative patients with a median overall survival of 17.2 months (95% CI: 13.9, 19.2) in the combination arm versus 8.9 months (95% CI: 6.7, 11.8) in the monotherapy arm (HR=0.62) in comparison to 12 months (95% CI: 9.4, 15.4) in the combination arm and 11.2 months (95% CI: 8.0, 15.4) in the monotherapy (HR=0.84) in hormone-receptor positive patients. An increased magnitude of effect in hormone receptor negative subjects was also observed for ORR. Similar findings were replicated in a number of studies.

The findings were replicated in a study comparing dual HER2 blockade versus single blockade, albeit with pertuzumab and not lapatinib (CLEOPATRA) and similarly in a study with trastuzumab emtansine versus trastuzumab on top of a taxane. Efficient HER2 targeting thus appears to change the behaviour of the tumour post progression. Mechanistic studies will therefore be conducted post licensure of this new indication aiming at explaining these findings.

Uncertainty in the knowledge about the beneficial effects

There was a concern of the inappropriateness of the control arm for subjects with hormone receptor-positive tumours since dual blockade (trastuzumab and lapatinib) has not been studied in comparison with hormone therapy in this population. Therefore the indication is restricted to patients with hormone receptor-negative tumours.

Data from exploratory analyses were suggestive of an increased overall benefit (PFS, OS, ORR) for subjects with serum HER2 ECD concentrations >15 ng/mL. However, serum HER2 ECD has not been confirmed as predictive of activity of dual blockade in any external study. Further data on biomarkers should be provided as an obligation to conduct post-authorisation measure.

Risks

Unfavourable effects

Adverse events were reported in similar proportions in the two treatment arms. In addition, a similarity in treatment-related AEs between the two treatment arms was observed. However, SAEs were more frequently reported in the combination arm compared to lapatinib arm. Furthermore, differences between the treatment arms with respect to specific AEs were observed. These included an increased frequency in the combination arm compared to the lapatinib arm of diarrhoea events and cardiac events though the majority were of toxicity grade 1-2 and transient. Hepatobiliary events were reported in similar frequencies in the treatment arms even though there was a difference in the number of reported events for the individual subjects between the arms. No major increase in reports on rash toxicity was observed when adding trastuzumab to lapatinib. A total of 17 subjects (11%) in the combination arm and 9 subjects (6%) in the lapatinib arm discontinued study treatment due to AEs.

After the exclusion of deaths due to disease progression, the numbers of fatal adverse events in the pivotal study were low and well balanced between the two arms.

Uncertainty in the knowledge about the unfavourable effects

The number of patients ≥ 65 years included in the pivotal study is limited (n= 37 (12%)). Patients in the elderly population present with an increase in concurrent medical conditions and are therefore expected to exhibit more adverse events although major differences may not be anticipated. A meaningful comparison of the rate of AEs, AEs leading to discontinuation, SAEs, and fatal AEs in the pivotal study, is not possible in this age group. The fact that there are limited data on the use of Tyverb in combination with trastuzumab in patients aged ≥ 65 years is reflected in the SmPC.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

While the modest improvement in PFS observed the ITT population for the combination of trastuzumab and lapatinib compared with single agent lapatinib might not be considered clinically relevant, the median OS benefit of 4.5 months is substantial and of clinical relevance for patients in this late-line of therapy.

Although the choice of the comparator might have led to an overestimation of the benefit of the combination therapy, this is not a concern for patients with hormone receptor negative tumours taking into consideration the magnitude of the OS benefit and in light of current practice. The difference in

median OS observed in exploratory analysis between the combination and monotherapy arms in this subgroup is considered clinically relevant. However, the benefit in patients with hormone-receptor positive tumour is questioned due to the lack of comparative data with endocrine-based therapy and considering the results from subgroup analyses. Thus the indication is restricted to patients with hormone-receptor negative tumour.

Regarding the safety of the combination lapatinib and trastuzumab, adverse events were common and an increased frequency was reported in the combination arm. Particularly, the incidence of cardiac events including LVEF decreases was higher (7%) when lapatinib was administered in combination with trastuzumab versus the lapatinib alone arm (2%) in the pivotal trial in the metastatic setting. However, the majority of adverse events were transient grade 1-2 events and manageable. No new safety signal was detected and the adverse events were consistent with the known safety profiles of both trastuzumab and lapatinib.

Benefit-risk balance

A major survival gain was reported in the pivotal study for patients receiving the combination lapatinib and trastuzumab. Although limited, the PFS results (primary endpoint) were in broad agreement with the OS and the apparent discordance in terms of magnitude of the effect should not have an adverse impact on the validity of OS results. The same applies to the results of the subgroup analysis in patients with hormone receptor negative disease where a PFS benefit of approximately 2 months (although not statistically significant) and a significant OS improvement of approximately 6 months were observed.

With regards to the safety of combination of lapatinib with trastuzumab no new safety signals were identified in the overall population. The slight increase in the incidence of SAEs is outweighed by the clear clinical relevant effect in terms of overall survival.

Based on the available efficacy and safety data, the CHMP considers that the observed benefits outweigh the tolerability of lapatinib in combination with trastuzumab.

Discussion on the Benefit-Risk Balance

Based on the available efficacy data and considering the report from the SAG, the CHMP concludes that the reported survival benefit is of clinical relevance and attributable to the activity of lapatinib in combination with trastuzumab.

Explanatory data on the role of biomarkers will be collected in a post-authorisation study to evaluate whether treatment with lapatinib in combination with trastuzumab could modulate the behaviour of the tumour post-progression.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 25 out of 29 votes, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include treatment for adult patients with breast cancer whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease, that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy. As a consequence sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated accordingly. Changes were also made to the PI to bring it in line with the QRD template version 9 and make minor corrections. In addition, the list of local representatives in the PL is revised to add contact details for the representative of Croatia.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following amended conditions:

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To present data in patients with hormone receptor-positive metastatic breast cancer, not currently intended for chemotherapy, and previously treated with trastuzumab from: 1. A randomised and controlled clinical trial (EGF114299) in a patient population essentially identical to that of EGF30008 except that subjects must have received prior treatment with trastuzumab, with aromatase inhibitor (AI) + trastuzumab included as the reference arm. Final clinical study report	May 2018

2. Approximately 70 patients from study EGF114299 who have been randomised to the lapatinib + AI arm with an exposure of approximately 6 months. The clinical study report (70 patients) should include the following data: Demographic and baseline characteristics, Disease characteristics, Prior anti-cancer therapies, Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Serious Adverse Experiences (SAE)s	June 2014
To present an updated analysis of survival for the mature dataset for study EGF30008	December 2013
To evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy	June 2018

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO)	December 2014

APPENDIX 1

DIVERGENT POSITIONS

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the extension of indication variation for Tyverb (EMEA/H/C/000795/II/22).

The reasons for divergent opinion were as follows:

1. The use of lapatinib as active comparator is highly questionable, as the drug is not approved as monotherapy in the sought indication, and it is considered not to be among the currently best options of care available for these patients in the clinical setting. It is thus not possible to soundly evaluate the magnitude of the effect and clinical relevance of the combination lapatinib + trastuzumab in the sought indication.

2. There are uncertainties on the reliability of the reported Overall Survival (OS) benefit in view of the modest Progression Free Survival (PFS) gain (4 weeks). It cannot be excluded that the results on OS are highly overestimated or that this is a chance finding.

3. The restricted indication in patients with hormone receptor (HR) negative is based on a post-hoc subgroup analysis that showed a larger effect on median OS on the basis of the HR status. However, no robust rational supporting a differential effect of the dual blockade of HER2 in HR negative patients is available. The results of the subgroups analysis can only be considered to generate hypothesis and are inadequate to define the target population.

Based on the above, the benefit-risk balance in the claimed indication cannot be considered positive.

London, 27 June 2013

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Daniela Melchiorri Pierre Demolis

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Barbara van Zwieten-Boot Hubert Leufkens